Diabetes in sub-Saharan Africa – from clinical care to health policy

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Lancet Diabetes and Endocrinology Commission Report

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Executive summary

Rapid demographic, socio-cultural, and economic transitions are driving increases in the risks and prevalence of diabetes and other non-communicable diseases (NCDs) in Sub-Saharan Africa (SSA). The impact of these transitions and their health and economic consequences are evident. While in 1990 the leading causes of death in SSA were HIV/AIDS, lower respiratory infections, diarrheal diseases, malaria and vaccine preventable diseases in children, in more recent years, cardiovascular diseases and their risk factors are replacing infectious diseases as leading causes of death in the region, and rates of increase of cardiovascular risk factors are predicted to be greater in SSA than in other parts of the world. Thus SSA – which contains a high proportion of the world's least developed countries – will face the multifaceted challenge of dealing with a high burden of infectious diseases and diseases of poverty, whilst also addressing an increasing burden of cardiovascular disease and its risk factors. At current time, many of the health systems in SSA struggle to cope with infectious diseases. Meeting the goals of the United Nations (UN) high level Commission on NCDs – to reduce premature mortality from NCDs by 25% by 2025 - and Sustainable Development Goals (SDG) – of reducing by 1/3 premature mortality from NCDs by 2030 – requires a coordinated approach within countries which starts with a firm consideration of burden, needs, and priorities.

Diabetes is an exemplar cardiovascular disease risk factor in that its prevalence tracks the transitions that lead to its precursors, obesity and overweight; untreated, it leads to a plethora of complications – both micro and macrovascular – which affect multiple physiological systems; and it closely associates with other cardiovascular risk factors – hypertension and hypercholesterolaemia – which interact to exacerbate risk of adverse outcomes. Diabetes, thus requires an interconnected, broad-based health system for effective management. Therefore improving the processes of care for people with diabetes should lead to health-systems improvement for many other conditions. If left unchecked, however, the adverse outcomes of diabetes and other cardiovascular risk factors could overwhelm health systems in SSA and leave many of sufferers with substantial morbidity and mortality. In addition, the interaction between diabetes and infectious diseases, further increase the burden of illness on resource constrained weak health systems.

With this recognition, *The Lancet Diabetes & Endocrinology Commission on Diabetes in sub-Saharan Africa* was formed to ascertain current burden of the disease, its risk factors and outcomes in the region, assess health system challenges in dealing with the burden, and to suggest potential solutions. We present the Key Messages of the Commission below, and also suggested operational targets (Panel 1) to help countries at all stages of development to transition to a state where the UN and SDG goals are achieved, if not surpassed.

1) True burden of diabetes (of all types), other cardiovascular risk factors, and macro and microvascular outcomes in sSA is unknown

Estimates from those countries region where high-quality data are available suggest that the rise in prevalence of diabetes, other cardiovascular risk factors, and adverse outcomes CVD is large and expected to further increase. However, most countries lack data and data collection systems that are reliable enough to enable a commensurate health system response to be mounted. To plan such a response requires high quality population-representative data on both current burdens and associated demographic factors, and to put in place systems for longitudinal data collection. It is also imperative to ascertain which tests and cut-offs for hyperglycaemia are most appropriate to use to define diabetes in populations in the region to prevent over or under treatment.

Knowledge of burden of type 1 diabetes is particularly important given that this condition is fatal without treatment which is relatively cheap and simple to administer.

2) Diabetes and its consequences are costly to patients and economies

We estimate that in 2015, the overall costs of diabetes in the region was $19.45 billion or 1.2% of cumulative GDP. Around 55.6% ($10.81 billion) of this arose from direct costs with out-of-pocket expenditures likely to exceed 50% of overall health expenditures in many countries. We estimate that the total cost will increase to between $35.33 billion (1.1% of GDP) and $59.32 billion (1.8% of GDP) by 2030. Putting in place systems to prevent, detect, and manage hyperglycaemia and its consequences is therefore warranted from a health economics point of view.

3) Health systems in countries in SSA are unable to deal with the current burden of diabetes and its complications.

Using information from the WHO Service Availability Readiness Assessment surveys, World Bank Service Delivery Indicator surveys, and the local knowledge of Commissioners, we found inadequacies at all levels of the health system which would be required to provide adequate management for diabetes, associated risk factors, and sequelae. We document inadequate availability of simple equipment for diagnosis and monitoring, a lack of sufficiently knowledgeable health care providers, insufficient availability of treatments, a dearth of locally appropriate guidelines, and next-to-no disease registries. This results in a substantial drop-off of patients along the diabetes care cascade with the largest proportion of patients going undiagnosed and those who are diagnosed not receiving advice and the medication they need. We also note scarce facilities to deal with the micro and macrovascular complications of diabetes. Additionally, despite calls for adding diabetes and other cardiovascular risk factor care onto extant infectious disease programs – such as HIV – we found little evidence that such programs are successful at improving outcomes.

4) At the current time, scarce health-care resources should be focussed on managing diabetes and other risk factors with a view to prevent complications

Managing diabetes and its fellow risk factors is relatively simple and inexpensive. Treating complications, however is costly, requiring providers with a high level of skill and specialised equipment. Preventing complications is therefore crucial. To allow this to happen effectively, de-centralisation in care – from experts working in hospitals to Community Health Workers and other non clinical providers working in the primary care system and delivering home-based screning and care - needs to be accelerated. Simple and effective information technology solutions should be utilised to enable more locally delivered care. An additional consideration is whether it is more beneficial to treat each risk factor associated with diabetes to pre-defined targets, or to consider risk factors collectively and aim to reduce over-all risk. For both the prevention of macro and microvascular risk factors, we found it more effective and more cost effective to consider treat risk factors as a whole, using benefit-based tailored treatment, rather than to treat each individual cardiovascular risk factor to target.

5) There needs to be more evidence on the benefits and risks (to both individuals and health system's ability to provide care) of screening before programs are rolled out across Africa.

The benefits of screening, especially in people who are deemed to be at high risk, seem obvious – earlier detection and management of diabetes and its risk factors and prevention of costly complications. However, as yet, there is no evidence – at least from high income countries, where studies have been done - that screening programs are effective at reducing adverse outcomes. Additionally, the thresholds for diagnosing diabetes (i.e.: the level of glycaemia that is associated with risk of adverse outcomes in the long term) and the best test to use are not defined for populations living in Africa. Hence any screening program that is started should only be done as part of a rigorous longitudinal outcomes study that also compares differing tests for diagnosis of hyperglycaemia.

Panel 1:

When health resources are severely limited difficult choices often have to be made in the face of competing priorities. Our review of the challenges involved makes it clear that models of diabetes care designed for use in countries with more advanced economies may be neither appropriate nor affordable in low-or middle-income countries. We advocate the pursuit of a utilitarian approach to the provision of diabetes care in most African settings – with widely available cheap treatments for prevention of complications in combination with strong public health measures to prevent an increase in obesity and diabetes. In this way investment in prevention of the consequences of diabetes will prevent the necessity of investing in wider scale availability of expensive treatments to manage the complications. Rigorous health systems research and implementation science (1) accompanying the introduction new treatments or management strategies is absolutely key to ensuring that solutions are both fitting to a local environment and that results are captured that

can be of use to other countries. Funding for this type of research urgently needs to increase. Bearing this in mind, we suggest a possible hierarchy of needs assembled on the basis of implementing strategies known to work in other settings. This hierarchy is based on the Commissioners' vast experience both in clinical care and in health system improvement, and our review of the literature during the process of this Commission. The principles are straightforward: each intervention should be evidence-based, effective, accessible, integrated and affordable. Of key importance, the Commission calls for services for provision of care and diagnostics for diabetes, its fellow risk factors, and its complications to be fully integrated, to minimise the indirect costs to the patient of having to attend multiple clinic appointments.

The prerequisites for launching therapy are education and structure. The aims of education are achieved at a personal, community level, and healthcare provider level. At a personal level, the aim is to make the patient an active informed partner in her own therapy rather than its passive recipient. At the community the aim is increased understanding and awareness of diabetes and elimination of prejudice. Education of medical personnel is needed to raise awareness of the disease, the simplicity of its treatment, and also to counterbalance marketing and medical education campaigns by the pharmaceutical industry, typically slanted towards use of more expensive patented forms of treatment. An appropriate structure for health care delivery which is embedded within the health system is equally essential.

We have considered necessary care needs in terms of level of service provision development of countries. We progress from care which we consider to be essential and we recommend should be present in 100% of countries by 2020; to care, which we consider should be the next step when level one care is achieved and should be available in 75% of countries by 2020 and 100% by 2025; and finally, level three care, which should be considered optimal and in place once other targets have been achieved. We recommend that this level of care is present in 50% of countries by 2020, 75% by 2025 and 100% by 2030.

Insert Table – operational targets to 2030

Introduction

Sub-Saharan Africa (SSA) is experiencing an estimated rapid rise in the prevalence of non-communicable diseases (NCDs). Although, in 2015 Africa was the only continent in the world where morbidity and mortality from infectious diseases still outnumbered those from NCDs, this balance will soon change as SSA experiences the full blown impact of rapid rise in NCDs. (2)

Rapid demographic (growing and ageing population), socio-cultural (lifestyle changes and eating habits) and economic transitions (higher income, urbanization, changing food availability, and evolving lifestyle and work practices) (3, 4) are driving sharp rises in the risks and prevalence of diabetes mellitus (diabetes) and other cardiovascular disease (CVD) risk factors. In SSA, between 1990 and 2010, BMI had increased more than 200%, and fasting plasma glucose by 80%, while the disease burden attributed to diabetes, as measured by disability adjusted life years (DALYs) rose by 88%. (5) More than 90% of diabetes cases in SSA are type 2, suggesting that modifiable risk factors are the major contributor to the burden of disease.(6)

Against this backdrop of dramatic statements sits the uncomfortable reality that most of the estimates for diabetes, other CVD risk factors, and CVD burden per se in countries in SSA are modelled from generally poor quality evidence using methods of defining diabetes that have been developed in high income countries often using European populations. In the case of diabetes, a recent study found that nationally representative empirical biomarker data on diabetes diagnosis is only available in a quarter of the 48 countries in the regions.(7) So, whilst there is reasonable evidence that diabetes and other CVD risk factors are increasing, the certainty of the situation is far from clear. In addition, the majority (34 out of 48) of the world's least developed countries are in SSA. (8) Thus, even though the focus of development aid and research funding has so far been infectious diseases (9, 10) many countries are struggling even to develop health systems to cope with an existing infectious disease burden which is much better delineated than CVD and its risk factors. It therefore seems an impossible task to ask them – as has been requested by the SDGs and UN High Level Commission on NCDs (11) – to respond to an, as yet, not accurately quantified burden of CVD risk factors, using methods yet to be proven to be effective in the region, and with little funding to do so.

Driven by this recognition, a group of academics, policymakers, and clinicians met at the Rockefeller center in Bellagio, Italy, in March 2015 to discuss the state of play and potential routes forward. We centered our discussions on the preventable CVD risk factor, diabetes, because of its multisystem interactions and adverse outcomes and necessity for broad based healthcare system improvements to manage it. We formed *The Lancet Diabetes and Endocrinology* Commission on Diabetes in SSA. Here we present the findings of the the Commission which includes discussion of burden, clinical, economic, and broader health systems, in order to inform the development of an effective response.

Methods

After the Bellagio meeting, the Commissioners organized into working groups to look at both the clinical and health systems elements involved in diabetes and diabetes care in SSA. Commissioners again met at the World Diabetes Congress in Vancouver in November 2015 to discuss progress. The final Commission meeting was held at the Harvard Dubai Centre, Dubai, in February 2016 to report results, discuss areas where we had found equipoise and to agree on the best approaches to advise in these areas, and to structure the report. Methods for sections of the report involving novel research can be found detailed in the appendix. The narrative sections of the report have been informed by extensive reviews of the literature and the knowledge and opinions of the Commissioners.

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Burden of diabetes in SSA

Globally, and according to NCD-RisC, the number of adults with diabetes rose from 108 million in 1980 to 422 million in 2014. (12) This translates to an increase in worldwide prevalence of diabetes of 80.9%; from 4.7% in 1980 to 8.5% in 2014 burden. (13) By contrast, diabetes prevalence in the WHO Africa region rose by 129.0% (from 3.1% in 1980 to 7.1% in 2014) See table 1. (14) This increase is second only to the WHO Eastern Mediterranean Region, where the prevalence rose by 132.2%, from 5.9% in 1980 to 13.7% in 2014. See table 1 for a comparison of change in prevalence rates over time in each WHO global region.

Table 1

Unfortunately, the various estimates of the diabetes prevalence in SSA have used different methodologies, all of which have limitations (see panel 2), hence there is no clear data on prevalence in the region – which is important for planning an adequate health systems response. As well as WHO and NCD-RisC, other well cited estimates come from the International Diabetes Federation (IDF) (15), and the Global Burden of Disease (GBD) group at the Institute for Health Metrics and Evaluation (IHME) (5), which has produced estimates of deaths and DALYs due to diabetes. However despite difference in methodologies, all sources point to there being a increasingly large burden of diabetes in SSA.

Whilst recognising the limitations of the methods (panel 2), the estimates used in this report are those of the NCD risk factor collaboration (NCD-RisC) (12), unless otherwise stated. We have chosen these estimates as they have been adopted by WHO and are likely therefore to gain global credibility.

Panel 2

Estimating prevalence of DM in SSA

There are several different estimates for the prevalence of diabetes in countries in the SSA region, each vary depending on the methodologies used to ascertain the diagnosis, for example, self-

report vs biomarkers, and within the biomarker group, which method was used; fasting glucose vs 2 hour oral glucose tolerance test (OGTT) vs HbA1C. Even in well studied HIC populations there continues to be debate about which biomarker most reliably predicts long term macro and microvascular outcomes of hyperglycaemia, and hence which should be used to diagnose the condition. (16, 17) There have been no longitudinal studies done in Africa to ascertain the best method of diagnosis. Thus whether HIC-developed methodologies for prevalence of diabetes can be used to reliably predict future burden of clinically relevant outcomes in SSA populations is currently unknown. Studies in this area are urgently needed.

Compounding this uncertainty is that many countries have used the WHO STEPs methodology to estimate burden (18) which has included use of fasting glucose to diagnose diabetes. This inclusion could potentially miss patients who are in the earlier stages of the disease and would manifest impaired glucose tolerance shown by a high 2h blood glucose on OGTT, but have normal fasting levels. The effects of these differences in methodology on cross-sectional prevalence estimates of diabetes have been demonstrated in African as well as in other settings (19). For example, prevalence of diabetes in older people in Africa was greater when measured by 2h OGTT than by measurement of fasting glucose alone (23.9% vs. 10.9%), and in non-STEPS than in STEPS studies (17.1% vs. 9.6%).(20)

Results are also affected by the sampling methodology used, with many country estimates coming from samples of convenience rather than those employing robust methods of sampling. Sample sizes also varies greatly between studies, for example, in the NCD-RisC study, some countries have fewer than 150 data points and others have tens of thousands (12). Geography and demographics also should be taken into consideration when interpreting results. For example, there are major gradients between the prevalence of obesity and diabetes in populations or cohorts containing young or older people (20); and although high quality data on urban versus rural prevalence of diabetes and obesity are lacking from countries in SSA, studies done in other countries clearly show differences in prevalence between rural and urban areas, and a change in that distribution over time (21). Additionally detection bias should be considered, whereby underdeveloped health systems in countries in SSA may lead to under-reporting of diabetes prevalence in comparison with HICs where diabetes is more reliably detected.

These factors need to be taken into consideration when interpreting all studies of prevalence in countries SSA. Additionally, and importantly, all of the studies producing estimates for the region as a whole – and individual countries within that region - are modelled, and often based on little or no data. Even though we have chosen to use estimates from NCD-RisC (12) for illustration, and recognise that the paper has utility in making comparisons across regions and over time, the prevalence data for individual countries from SSA presented in that paper is of questionable reliability. (22-24) 21 countries in SSA had missing data and in those countries with data, samples were often small and data old.

The increasing impact of diabetes in the region is reflected in results from the 2015 GBD study, which estimated that diabetes in SSA caused an average of 118,758 deaths and 3,757,054 DALYs; between 1990 and 2010 DALYs attributable to diabetes rose by 88%.(5) There is inevitably considerable imprecision in such estimates and other groups have produced different figures. For example, the IDF estimated that in 2015, around 321,000 deaths in SSA were attributable to

diabetes, and 79% of these deaths occurred in persons aged 60 years or less – a proportion higher than any other region in the world.(15)

Diabetes in Africa

Type 2 Diabetes

As in other parts of the world, over 90% of people living with diabetes in SSA are considered to have Type 2 diabetes, (6, 25) classically associated with increasing age and overweight and obesity. Given that the majority of cases of diabetes in SSA are type 2 diabetes, throughout the report we refer to type 2 diabetes simply as diabetes with other types of diabetes being specified.

Drivers of diabetes

1) Overweight and obesity

Traditionally 'lifestyle factors' leading to overweight and obesity and thence onto diabetes were considered modifiable. However, it is now increasingly acknowledged that, at least on the individual level, lifestyle drivers of diabetes are difficult to modify; individuals have far less agency than was previously thought (4, 26). Additionally, genetic predisposition to overweight, obesity, and diabetes, once thought to be relatively stable over geological timeframes, is now seen to be more modifiable in the short term than previously thought, via intergenerational, epigenetic changes. Although there are varying degrees of susceptibility to diabetes and its antecedents, most is infinitely preventable (modifiable) given appropriate policy interventions.

Although not all people with diabetes in Africa are overweight and obese by western standards, a rapid increase in the prevalence of overweight and obesity is undoubtedly a major driver of the increasing prevalence of type 2 diabetes in the region [NCD-RiSc/GBD]. The contribution of overweight and obesity to the variance of the prevalence of diabetes in Africa is an as yet unanswered question; some studies suggest that African populations might develop diabetes at lower levels of body mass than people of European origin, (27, 28) and other studies have suggested that for the same level of obesity, African populations are at lower risk for diabetes than their Western counterparts (29, 30). But high quality, convincing evidence is lacking.

Globally, overweight and obesity was traditionally considered a disease of urban, rather than rural populations, although this situation is now in transition, and certainly in higher income countries, overweight and obesity is seen more in rural populations (21, 31). Few high quality longitudinal studies have been performed in Africa, but those that have been done suggest that overweight and obesity rates have increased in urban areas. For example, Ziraba et al (32) used data from Demographic and Health Survey (DHS) studies done between 1992 and 2005 in 7 African countries to show that overweight and obesity had increased by 35% in women living in urban areas, and that 31.4% of urban women were now overweight or obese, with a range from 28-29% in Burkina Faso and Senegal to 38% in Kenya. However, it seems that the picture in the region is mixed; some countries show a greater prevalence of overweight and obesity amongst urban dwellers whereas some show a greater prevalence in rural districts. (33) This mixed picture is likely partly explained

by difference in the pace of the on-going rural transformation across Africa (34). See Panel 3 for the Commission's analysis on the interactions between diabetes and obesity in countries in SSA.

Overweight and obesity is associated with low SES in high-income countries and high SES in low and middle-income countries; known as the "reversal hypothesis". (35) While this observation holds true in aggregate, greater variation has emerged at a more granular level and likely also depends on definitions of SES employed by studies. For example, within SSA Ziraba et al (32) found that overweight and obesity was more prevalent in women of lower socioeconomic status, with the most rapid increase (50% overall) seen in the poorest urban dwellers, whereas levels declined by 10% in women with secondary education or higher. Others, however, (36) found no effect of education in two African countries, and a small, cross sectional study in rural Uganda suggested that obesity was a greater problem amongst those of higher SES than those of lower SES (37). (37). In a recent study, Manne-Goehler et al. found a strong education gradient in the self-awareness of overweight and obesity, suggesting that in the long-term education and high SES may be associated with lower levels of this risk (7)

Such heterogeneity in results comparing urban and rural, high with low SES are to be expected in a rapidly changing environment, but paucity of high quality studies examining the issues limit any firm conclusions about links between place of residence, SES, and drivers of obesity. Lack of reliable information additionally limits the ability to suggest appropriate interventions.

Poor nutrition in fetal and early life, which is known to contribute to obesity related health problems in later life, especially when combined with subsequent abundance of food - the so-called "thrifty phenotype" (38) - is a likely problem for Africa (30). Some high quality evidence for this is beginning to emerge from the region. For example, a study of 352 Malawian children (median age 9.3 years) who had been treated for severe acute malnutrition at an average age of 24 months showed them to have clear evidence of "thrifty growth" as compared with sibling and community controls, despite evidence of catch-up. (39). Further research is needed to assess the long-term impact of intra-uterine and childhood malnutrition in Africa.

Cultural factors also have influence on rates of overweight and obesity, for example, a larger girth is perceived as a sign of affluence and is a deeply rooted status symbol conferring influence, health, and attractiveness. (40) Excess weight also has positive connotations in societies in which a strong stigma is attached to weight loss and wasting associated with HIV/AIDS (6).

2) Population trends and ageing

The population aged 20-79 years in SSA is projected to increase from 441 million in 2015 to 926 million in 2040 (41), and given the association between diabetes and age, this will be one of the important drivers of the increase in the numbers of people with diabetes. Furthermore, increasing longevity is a notable feature of populations within SSA, especially in countries with high HIV prevalence and where life expectancy is increasing with roll out of ARVs. [ADD TLDE Geldsetzer, Davies, in press]. Although large scale high quality studies from the region are scare, a recent systematic review of studies published between 2000-2015 estimated a prevalence of 13.8% (CI 13.2-14.3%) in those aged 55 years or more. (20) Given the potential impact of an ageing

population on the prevalence of diabetes in SSA, it is essential for health system planning that high quality, local information is obtained on the relationship between ageing and diabetes.

See panel 3 for the Commission's analysis of the relationship between diabetes and age in countries in SSA.

Panel 3

Commission estimates of prevalence of obesity and diabetes in SSA: empirical analysis of national surveys

While many studies have estimated the prevalence of diabetes and obesity in SSA, few empirical analyses at country level exist. We estimated the prevalence of diabetes in 10 countries using individual level participant data from 10 nationally representative surveys to obtain an up-to-date estimate. The surveys included the WHO Stepwise Approach to Surveillance Surveys (STEPS) undertaken in 2005-2013 in Benin (2008), Comoros (2011), Guinea (2007-08), Liberia (2011), Mozambique (2005), Tanzania (2012), Togo (2010) and Seychelles 2013), a Demographic and Health Survey undertaken in Namibia in 2013, and the South African National Health and Nutrition Examination Survey undertaken in 2012.

The data sources and methodology are discussed in detail elsewhere and a summary included in appendix A.(7) Our efforts to obtain collectively from WHO data from the STEPS surveys conducted across Africa, were unsuccessful. (24) We therefore independently approached each country directly. The complete pooled dataset included 39,062 individuals across 10 countries over the period from 2004-2014.

The analysis reveals a strong relationship between increasing age and the prevalence of diabetes and obesity, with higher prevalence for women across all age groups. Cross- country prevalence of diabetes ranged from 1.3% in Benin to 21.6% in Seychelles based on fasting blood glucose measurement and self-reported use of diabetic medications (Figure 1). Age stratified prevalence level of diabetes revealed rising prevalence levels with age, with levels reaching around 30% in men and women aged 55-64 years in South Africa and Seychelles (Figure 1).

Figure 1

Obesity levels (body mass index >25 kg/m^2) also varied across countries, with age-stratified levels ranging from less than 10% in men aged 25-39 years old in Benin and Togo to more than 70% in South Africa and almost 80% in women aged 55-65 years (Figure 2).

Figure 2

Panel 4

Genetic drivers of diabetes

We are not aware of any initiative which has successfully integrated genetic markers into clinically utilisable risk prediction scores (especially in LMICs) or used genetics to successfully improve treatment outcomes in diabetes. Nevertheless genetics continue to be an area of interest both to funders and researchers. We question the need for such research investment in a geographical area where even burden of disease goes unknown. However, given the interest in the area, and the suggestion – although unproven – that knowledge of genetic susceptibility to diabetes might help define the scale and direction of diabetes epidemic in Africa we present a brief overview of the field in SSA.

In global populations, nearly 80 genetic loci have been implicated in susceptibility to type 2 diabetes (42) and about 50% of these risk loci were replicated in a recent study conducted among SSA enrolled in the AADM study (43, 44) (PMID:26635871). This replication results suggest that the genetic architecture of T2D in SSA is likely characterized by several risk loci shared with non-African ancestry populations and that genetic data from Africans promises to inform the genetics of all human populations.Epigenetic changes are also known to have differential effects on diabetes incidence dependent on population studied, and may be very important in African populations, given early life risks (45). Studies in Sub-Saharan African populations suggest that there has been natural selection for a range of genomic regions associated with obesity and type 2 diabetes, and a study that mapped the genetic risk of type 2 diabetes by measuring the allelic frequency of 16 associated variants in 51 populations suggested that Africans face the greatest known genetic risk for type 2 diabetes (46) Some knowledge gaps can also be filled by the study of African-American populations, although such comparisons must be interpreted with caution, since African-Americans mostly originated from West or Central Africa and are not representative of SSA as a whole, or indeed of their own parent populations. (47) It is nonetheless clear that African-American populations have a two-fold risk of type 2 diabetes compared with those Americans of European extraction (48, 49), and also have a much higher current prevalence of type 2 diabetes than most African populations (12). This may be an indication of future trends in Africa. Numerous initiatives linking genetics and cardiovascular risk are underway in SSA, the H3Africa (http://h3africa.org) and RODAM (Research on Obesity and Diabetes among African Migrants) (http://www.rod-am/eu/content/objectives) studies are two examples.

Genetics of type 1 diabetes in Africa

Little is known about the genetics of T1DM in SSA. However, a study done in African American populations (50) showed large diversity of HLA DRB1-DQA1-DQB1 haplotypes and genotypes in African compared with European descendants. Association analyses reproduced a number of type 1 diabetes risk effects seen in European-derived haplotypes, whilst additionally showing novel effects for African-derived haplotypes. In particular, the African-specific “DR3” haplotype DRB1*03:02-DQA1*04:01-DQB1*04:02 was protective for type 1 diabetes. (50). Additionally, the DR4/DR9 genotype, which contains an African-derived “DR9” haplotype, confers an odds ratio of 30.88, comparable to the highest risk genotypes found in European origin populations.

Panel 5 Gestational diabetes

Relative insensitivity to insulin is a normal feature of pregnancy and gestational diabetes (GDM) results when pregnancy results in overt hyperglycaemia. Since a fetus exposed to hyperglycaemia overproduces insulin, which can lead to macrosomia, obstetric difficulties may result (51) and adverse outcomes increase in linear fashion above the normal glucose range. In addition to that caused by GDM, hyperglycaemia in pregnancy may also be due to pre-existing diabetes, or to diabetes that manifests for the first time in pregnancy. Pre-existing diabetes increases the risk to the foetus over and above that of GDM.

BMI and gestational diabetes are highly correlated (52), and hyperglycaemia in pregnancy is becoming increasingly common in parallel with the increased prevalence of diabetes and obesity in the background population. Increasing global trends in maternal overweight and obesity have been reviewed extensively by Poston et al (52). Within SSA, however, demographic and Heath Surveys (DHS) show wide variation in the prevalence of obesity in women of childbearing age, with rates ranging from 0.7% in Madagascar to 26.8% in Lesotho. Although maternal underweight has previously been of great concern it is now less common than excess weight in women of child-bearing age in the region (53)

The global prevalence of hyperglycaemia in pregnancy was estimated at 16.9% in 2013, equating to 21.4 million live births. More than 90% of cases were estimated to occur in low and middle-income countries, and 16.0% were attributed to pre-existing diabetes or diabetes manifesting for the first time in pregnancy, leaving around 64% due to GDM. However, it should be borne in mind that prevalence may vary by region according to the diagnostic criteria used. (54) Unfortunately, studies reporting on the relative numbers of the causes of hyperglycaemia in pregnancy from countries within SSA are rare.

There is little information on the prevalence of GDM in the SSA region. A recent systematic review found a prevalence of GDM ranging from 0% (Tanzania) to 13.9% (Nigeria). (54) The authors comment that “it is alarming that very little appears to be known about GDM in Africa”, and only 6 countries (5 in SSA) provided data of sufficient quality for inclusion in this review. In addition, diagnostic criteria differed between studies and higher prevalence was seen in studies done after the year 2000 and in those which used more current diagnostic criteria. Diagnosing gestational diabetes

It is recommended that screening for GDM is carried out between 24 and 28 weeks of gestation, using the 75g OGTT. However, there are differences between organisations’ diagnostic criteria for GDM and, in addition, criteria for GDM have changed over time. (54) This makes drawing comparisons between studies and synthesising results from studies challenging, both within Africa and globally. For illustration, a study of around 1000 pregnant women screened for GDM between 24 and 34 weeks gestation in a single clinic in Nigeria using the OGTT (55), found prevalence of 3.8%, 8.1%, and 8.6% respectively when 1999 WHO (56), new 2013 WHO (57), and IADPSG (International Association of Diabetes and Pregnancy Study Groups Consensus Panel) criteria (58) were used.

After results of the HAPO study were reported, (59) many groups revised their guidelines. In particular the IADSPG and WHO 2013 (which is similar to the IADSPG) criteria differ from older criteria or those used by other organisations; only one abnormal value, rather than two, is needed to diagnose GDM and the fasting glycaemic thresholds used to diagnosed glycaemia have been lowered. (54) The new criteria will likely result in an increased prevalence of GDM, with knock-on effects on burden to health systems. For a full review of diagnostic criteria for GDM see Ma et al (51) It should also be noted that the HAPO study – on which the IADSPG criteria are based – looked at outcomes of hyperglycaemia in pregnancy in a non-African population and outcomes may be different in populations that are distinct from the original study population. (60) Further research is needed to ascertain whether the new WHO 2013 criteria are applicable to populations within SSA in terms of their ability to predict adverse maternal and offspring outcomes.

Risk factors for GDM in SSA, as elsewhere, are GDM in a previous pregnancy, family history of type 2 diabetes, previous still birth or child with macrosomia, and age >30 years. It is not entirely clear whether African women are at increased risk of GDM as compared with other ethnic groups. In a multi-ethnic society such as the USA, women from South-East Asia were found to develop GDM at lower BMI than women of European, Hispanic-American, or African-American origin, and it was estimated that two-thirds of GDM in African-Americans could be prevented if all women were of normal weight when they entered pregnancy. (61)

Complications of hyperglycaemia in pregnancy

Complications include pregnancy-induced hypertension and preeclampsia, ante-partum haemorrhage, complications of labour, preterm birth, birth trauma, congenital anomalies, and high perinatal mortality. (51, 52) Women with GDM are at high risk for developing subsequent type 2 diabetes and their offspring have higher susceptibility to glucose intolerance and obesity later in life. In addition, the risk of diabetic retinopathy during pregnancy is nearly twice that in the non-pregnant state. (62). Rate of complications is greater in pregnancies with pre-existing diabetes. (51, 52, 63)

Relatively little is known about the maternal or offspring outcomes of pregnancy in women with pre-existing diabetes in Africa, other than from a few previous studies which often are of small sample size or published years ago and with little relevance to the current situation in SSA (64)(65)(66) Given the increasing prevalence of obesity, and its associations with GDM or Type 2 diabetes, in women who are of reproductive age, the potential impact on both the women and their offspring could be enormous. That so little is known about these issues in Africa is cause for serious concern.

Treating hyperglycaemia in pregnancy in women in SSA may be no different to treating women in other countries. Of note, however, all studies that the Commission has identified on the management of hyperglycaemia in pregnancy in SSA populations have been observational; (65, 67-69) randomised controlled trials comparing agents in Africa urgently need to be done.

Type 1 Diabetes

Type 1 diabetes can occur at any age, but typically affects people younger than 40 with a peak onset around the time of puberty in Western countries; presentation at an older age (for example, 15-25 years) has been reported in Africa (70), however, given that type 1 diabetes is potentially missed in younger people in the region, it is impossible to say for what age group presentation is 'characteristic'. With increasing age, the clinical distinction between types of diabetes also becomes blurred, which further compounds the issue of ascertaining true lifetime prevalence of type 1 diabetes.

The incidence of type 1 diabetes began to rise in Western populations around the middle of the last century, and it is still increasing in many parts of the world. (71) The rapidity of this increase points to environmental causation superimposed upon genetic susceptibility. For example, Ethiopian immigrants to Israel developed type 1 diabetes at higher rates than their counterparts in Ethiopia. This is thought to be due to genetically predisposed individuals being exposed to new environmental triggers in Israel. (72). Earlier age of onset is associated with higher degrees of genetic susceptibility (see panel 4), and the secular trend towards earlier onset in western populations suggests increased penetrance of the disease; a similar shift has also been reported in Africa.(73)

Incidence varies widely with geography and a more than 350-fold difference in childhood type 1 diabetes between populations has been described (from an age-adjusted incidence of 0.1/100,000 per year in China to 36.8/100,000 per year in Sardinia). (74). One cannot therefore easily extrapolate incidence from one area to another. Unfortunately, information on prevalence and incidence from SSA is scarce. For example, estimates used in the 2015 IDF Atlas were extrapolated from studies in only five countries (Ethiopia, Nigeria, Rwanda, Tanzania and Zambia). From the existing evidence it seems that the incidence of type 1 diabetes in SSA is relatively low compared with many other parts of the world. But, poor quality, small studies, and the limited ability of health systems to diagnose sufferers means that the true prevalence remains obscure. (75) Recent evidence from Rwanda, however, suggests that the low apparent prevalence in SSA is very likely to represent failure of diagnosis or high mortality in diagnosed cases, as numbers rise sharply when interventions become available (76, 77)[Rwanda in country profile – see appendix]. An additional limitation of studies is that estimates have generally focused on children under the age of 15 years, therefore not accounting for a substantial proportion of people with disease onset after this age. The only published prevalence figure that covers the entire young adult age group is from Rwanda – 16.4/100,000 population <26 years. (78, 79) In Rwanda there are 3.5 times as many cases aged <26 years as <15 years.

Other forms of diabetes in Africa

Other forms of diabetes in the region may constitute a greater proportion of cases than the 5% seen in "Western" populations. (25). Of particular note, in Ethiopia, many cases of diabetes that had previously been considered to be type 1 are now being reconsidered in the light of antibody studies that have not shown presence of antibodies typical of the disease (70)

Malnutrition related diabetes has been reported from Africa, but its classification as a distinct subtype has been controversial, even given several cases reported in the literature. (40, 70) Also known as fibrocalculous pancreatic diabetes, it is usually seen in underweight, malnourished

patients, and is characterized by severe hyperglycaemia without ketosis, high insulin requirements, and lack of autoimmunity.

Variant forms of diabetes have been described in people of African descent since the 1950s. Reports from African-American populations indicate that the condition is seen in new-onset patients, typically middle-aged, overweight, and with a family history of type 2 diabetes in 80% of cases. Despite presentation with ketosis, such individuals can usually be managed without insulin. (80) The extent to which this represents a true variant form of diabetes remains uncertain, but it does show the need for more detailed investigation of the pathophysiology of diabetes in people of African descent.

Complications of diabetes

As discussed extensively in panel 2 there is not enough high quality evidence for estimates of burden of diabetes in SSA and trends over time to be reliable. The same is true when considering burden of complications. In particular, detection bias likely has a large impact on reporting of complications of diabetes in countries where health systems are not developed enough to provide services and health seeking behaviour is low. In addition, evidence points to the fact that hyperglycaemia in patients in SSA is detected at a later stage than in HICs (6), thus given the longer lead time of hyperglycaemia before treatment is given, patients in SSA may appear more susceptible to complications than their peers in other countries. A lack of data systems in many countries is a major hurdle to adequate documentation of complication rates; WHO found that only 17% of countries in the region had any form of diabetes registry, (although didn't report detail as to the geographical coverage or quality of information captured in those registries). (81) Additionally, the quality of the data that are reported will inevitable vary in line with the ability of health services to record and retrieve information relating to complications of diabetes.

In this section we have presented the highest quality evidence that we could find, but this should not be taken as a *de facto* representation of the actual state of play; the studies presented merely serve to illustrate.

Death

In 2015, GBD estimated that in SSA, diabetes contributed to an average of 145, 189 deaths (uncertainty interval 129 914 to 164, 809) or 1.8% [1.68-1.97%] of deaths in the region. (5). These figures should be interpreted with caution given the inadequate cause of death recording in the region. Indeed, given the prevalence of diabetes in the region and the inadequacy of many health systems to diagnose and treat diabetes and its complications effectively, this estimate seems very low.

Relatively little is known about the causes of death due to chronic complications of diabetes in SSA (6). This is due to the lack of vital registration systems in SSA and poor diagnostic facilities. Some countries within the region use verbal autopsies in sample populations to determine the cause of death, which give estimates at population level. A recent study from the INDEPTH network of Health and Demographic Surveillance (HDS) sites suggested that diabetes contributed little to NCD

mortality in Africa in comparison to cardiovascular diseases and cancers. (82) However, diabetes may not have been captured by this methodology as a contributor to death if not ascertained as a direct cause of death.

There is also a lack of data from the region on acute mortality due to diabetes, although the Commissioners' experience and opinion suggests that acute mortality in SSA is most often due to undiagnosed or inadequately treated type 1 diabetes, which rapidly progresses to DKA and death. Certainly, early reports from SSA document a very high mortality for type 1 diabetes. In Mali during the 1990s, 50% of patients died within two years, (83) and a study published in 2005 estimated life expectancy for children aged less than 15 years in Mozambique was 3.5 years; a child developing diabetes in a rural area was unlikely to survive for more than a year. (84) Data on mortality in people with T1DM from some other countries was a little more encouraging. In Soweto in South Africa, between 1982-92 the mortality rate was 16% over 10 years (with half the deaths from renal failure, and others from ketoacidosis, hypoglycaemia and sepsis), although, a follow-up study showed 43% mortality at 20 years' duration. (68) Recent data from Rwanda suggested a five-year survival of 93.8%. It is doubtful, however, that this data – where missingness was high and which could potentially subject to a Hawthorne effect – reflects the true state of affairs. It is possible that mortality could have been up to almost triple the crude mortality rate of 13.9 per 1,000 patient years. (15)

Even though reliable data from SSA are not available, the small number of studies that have been done can still be taken to reflect a state of care that is far below standards seen in more affluent parts of the world, where life expectancy for young people diagnosed with type 1 is now only a few years less than that of the general population. (85)

Chronic complications of diabetes

The chronic complications of diabetes affect blood vessels, and are conventionally subdivided into macrovascular and microvascular, but also impact upon other tissues including nerves and the optic lens (cataracts). Relatively little is known about the prevalence, age of onset, or rate of progression of diabetic complications in SSA, and most evidence comes from small, single country, single centre, and somewhat out of date studies. A systematic review with subsequent use of Global Burden of Disease methodology calculated that the non-fatal burden of disease in Years Lost due to Disability due to diabetes in South Africa in 2009 was 78,900 YLD in total; 64% from diabetes alone, 24% from retinopathy, 6% from amputations, 9% from attributable stroke disability, and 7% from attributable ischemic heart disease disability. (86) Additionally, GBD 2015 estimated that diabetes contributed to 5,556,560 (uncertainty interval 4,753,194 to 6,442,898) DALYs in 2013, which corresponded to 1.05 (0.94-1.16)% of all DALYs in the region. Such estimates are necessarily imprecise, and, as previously discussed, seem low, given the estimated prevalence of diabetes in the region and the lack of access to health systems for management of hyperglycaemia.

Lack of reliable data is a limitation highlighted in all reports of specific complications. For example, the authors of a recent systematic review of the prevalence chronic complications of diabetes in the region (25) could find only 23 studies to include. The recorded prevalence of retinopathy

varied from 7% in Kenya to 63% in South Africa; neuropathy from 27% in Cameroon to 66% in Sudan; and microalbuminuria from 10% in Tanzania to 83% in Nigeria. Macrovascular complications were not covered, and a search of the literature done by the Commission using terms diabetes and Africa and 'systematic review' and [complications OR macrovascular OR cardiovascular] did not return any results addressing the prevalence of cardiovascular complications. The most recent regional narrative review comes from Levitt et al in 2008 (6) who notes that ischaemic heart disease was less common amongst indigenous Africans with diabetes (5–8% based on ECG stress tests and 4% based on history) than in their counterparts of European heritage (23% based on positive history). They also note that there was little evidence on diabetes and stroke.

The information available does indicate that vascular complications manifest sooner after diagnosis of diabetes than in other parts of the world (6), an inevitable consequence of late diagnosis and poor glucose control. Thus if reliable evidence were available, we suspect that the prevalence and severity of complications of diabetes in the region would far surpass reports from HIC studies. A truly concerning deduction when considering that health systems in SSA will neither be able to cope with the numbers of cases of complications nor their severity.

Diabetic eye disease

The sight-threatening manifestations of diabetes: diabetic retinopathy, proliferative retinopathy, and maculopathy, are preventable and treatable before vision is lost.(87) Cataract is prevalent amongst patients with diabetes in Africa but much of the literature has focused on diabetic retinopathy, which is where our discussion will focus.

Globally, diabetic retinopathy accounts for 2.6% (2.2 to 3.4) of all blindness (88) and age-standardised prevalence of retinopathy as a cause of blindness has been found to be highest in sub-Saharan Africa, at 0.14% (0.10 to 0.20). The most recent systematic review on prevalence of DR in people with diabetes in SSA was published in 2013. (89) The authors included 62 studies from 21 countries in the region and, accepting recognised differences in diagnoses and sampling techniques, the prevalence in population-based surveys was 30.2 to 31.6% for diabetic retinopathy, 0.9 to 1.3% for proliferative diabetic retinopathy, and 1.2 to 4.5% for any maculopathy. The numbers are roughly similar to global reported prevalence (90) which is surprising given the lack of access to diagnosis and treatment for hyperglycaemia, but it is likely that poor access to health systems and reporting in African populations result in underestimation of prevalence.

Diabetic nephropathy

The contribution of chronic kidney disease (CKD) to global causes of death nearly doubled between 1990 and 2010, although improved ascertainment and ageing populations may have contributed to this increase (91). By 2010, 70% of patients with end-stage renal failure were estimated to live in low-income countries. Hypertension was the leading cause of death from kidney disease world-

wide in 2010 (91) but the number of attributable cases was falling by 2013, whereas cases attributable to diabetes were on the increase.(92)

The true prevalence of both chronic kidney disease (CKD) and diabetic nephropathy in SSA remains uncertain due to the lack of population-based surveys and diabetes registries. However, evidence from a systematic review and meta-analysis of studies involving 64,307 people estimated the prevalence of CKD in SSA at 13.9% (95% CI 12.2–15.7). The mean age was 41·4 years (SD 9·9). 46 494 (72%) had diabetes, 2765 (4%) were obese, 37 169 (58%) were HIV positive, and 7845 (12%) had hypertension. These findings should be interpreted with considerable caution, since only 3 of 90 studies were considered of high quality, and 80% of the analyses were hospital-based studies of patients with pre-existing conditions such as diabetes or HIV. In particular it should be noted that the estimated prevalence of diabetes fell to 6% in the 21 studies deemed of medium or good quality. (93, 94) Similar caution is needed when it comes to the prevalence of nephropathy in patients with diabetes, which has in most studies been based on the presence of proteinuria. A systematic review identified 32 studies from 16 African countries, only 2 of which were population-based. This study suggested rates of proteinuria as high as 95% at 10 years of follow-up, with an 18.4% mortality from nephropathy at 20 years of follow-up. (95)

Studies have shown that African-Americans have twice the risk of end-stage renal disease, as compared with whites, even after correction for socio-economic and clinical risk factors. This appears to be due in part to inheritance of an Apoprotein L1 (APOL1) gene variant, whose high prevalence in West Africa may have been driven by selection for the protection it confers against some variants of trypanosomiasis. (96) APOL1 has been associated with accelerated progression of several types of renal disorder, including the increased susceptibility to HIV-induced nephropathy, and might play a similar role in diabetic nephropathy. (97) When factors such as hypertension, HIV, genetic predisposition, and diabetes are combined, as is often the case, renal damage is likely to be accelerated. (98) In fact, the average age of onset of end stage renal disease in SSA is estimated to be 20 years younger than in those in Western countries.

Diabetic neuropathy and the diabetic foot

Diabetic peripheral neuropathy (DPN) is probably the most common complication of diabetes globally, affecting over 50% of those with diabetes (99, 100). However, estimates vary depending on the diagnostic and epidemiological methodologies used. DPN can be painless or, less commonly, painful. (101) Although, well designed, large, recent, population based studies are not available, and this section should be interpreted in light of that, published data from countries within SSA suggest that DPN is common in the region. (99) Whilst in the US the prevalence of diabetic foot ulcers was estimated to affect 8% of diabetic patients (102), the prevalence in SSA is thought to be higher. For example, in Tanzania it is estimated at 15% (103) in Cameroon 13% (104) and Nigeria 9.5% (105). In hospitalised patients, as would be expected, the prevalence is even higher again, although limitations of study size apply. The clinical features of painful DPN are similar to that encountered outside Africa and include poor quality of life, insomnia and depression (106).

Although, again, evidence is sparse and not recent enough for firm conclusions about current status to apply in SSA, peripheral neuropathy is believed to be the principal underlying risk factor for foot ulceration in diabetes patients (107, 108). This contrasts with high-income countries where peripheral arterial disease (PAD) is closely associated with development of the diabetic foot disease. (109) The pattern seems to be changing, however, with prevalence of PAD rapidly rising in the diabetic population in SSA. Compared with prevalence rates of less than 10% in the 1990s, recent studies show much higher rates of PAD of between 20-54% (110-112)

In addition to DPN and PAD, multiple environmental factors are associated with both the occurrence and severity of diabetic foot disease; for example bare-foot walking (which may be cultural or related to inability to afford shoes), ill-fitting shoes or rodent bites on feet particularly in those who sleep on the floor. (107, 113)

In SSA, amputations are frequent outcomes in those with diabetic foot ulcers. Around a third of these amputations have been reported to be associated with neuro-ischemic lesions and/or progressive infection. (114) The hospital mortality rate can be as high as 54% in those with severe foot ulcers (Wagner score >4) managed without surgery or amputation (115). Amputation rates may also be lower than expected as result of difficulty in obtaining consent for surgery. Sadly, some patients with severe diabetic foot ulcers discharge themselves from hospital against medical advice, putting themselves at high risk of severe sepsis and death at home.

Arterial disease

Cardiovascular disease is modulated by three major preventable risk factors other than smoking (which is increasing rapidly in Africa (116, 117)): hypertension, diabetes, and hyperlipidaemia. Although obesity largely manifests risk through its effects on these factors, it is still classed by many investigators as a modifiable CVD risk factor, and it thus included in this discussion. Between them, these risk factors are thought to account for the majority of deaths from cardiovascular causes. According to GBD, hypertension remains the leading risk factor world-wide, but diabetes (and obesity) replaced cholesterol in second place between 1980-2010 for all categories other than ischaemic heart disease, with the mortality burden shifting from high-income countries to low and middle-income countries (91). In SSA, obesity and hypertension are thought to be the most common cardiovascular risk factors (although issues of lack of reliable data apply). (118) We have previously discussed obesity. The prevalence of high blood pressure has increased rapidly over the past two to three decades and, according to the WHO STEPS surveys conducted in the region, the prevalence of high blood pressure ranges from 19.3% in Eritrea to 39.6% in Seychelles. (119). It is estimated that 150 million Africans will be treated for hypertension by 2025 compared to 80 million in 2010, an increase attributed to excessive alcohol consumption, reduced physical activity, and adoption of "Western" diets and other features of the economic transition. (119)

The extent of co-association of cardiovascular risk factors in individuals with diabetes is even less well known. Recent studies have estimated that among patients with diabetes in Africa, the prevalence of hypertension ranges from 44% to 76%. (120-123) Little is known about the prevalence of hyperlipidaemia in patients with diabetes in SSA, and the prevalence of metabolic syndrome among African people with diabetes in clinical settings ranged from 25% to >90% depending on the definition criteria used. (124) Lack of high quality information is also a major limitation when reviewing the features of people presenting with cardiovascular disease in SSA. For example, a systematic review of myocardial infarction in the region found only 7 studies from

five countries that satisfied all inclusion criteria (125). Nevertheless we have presented some of the literature to illustrate the heterogeneity of risk factors in patients presenting with coronary disease; 41-66.3% for hypertension; 22.5-40% for diabetes; 8.8-67.3% for hyperlipidaemia; 11.8-44% for smoking and 27-80% for obesity. Sample size was exceedingly small in all these studies, ranging from 30-169, likely reflective of the inadequacy of record keeping and storage (126)

A concerning feature of the changing pattern of CVD in Africa is the proportion of deaths under the age of 70 years, which are still increasing in SSA whilst falling in many HICs; attributable deaths under age 70 contributed 21% of the total in high income countries but 58% of the total in SSA. (5) Thus CVD seems to be affecting younger, more economically productive people in SSA as compared with HICs.The scale of the cardiovascular epidemic likely to affect Africa awaits clearer definition, and so too does the pattern. But cerebrovascular disease is likely to contribute substantially to the burden of cardiovascular disease given that it is thought to be responsible for around 11.23% (CI 10.92 to 11.57) of all deaths worldwide. (5) Stroke is potentially preventable, and a systematic review of world-wide stroke incidence showed a 42% reduction in incidence in high-income countries over the four decades from 1970 to 2008. In contrast, the incidence of the condition has increased by 100% in low and middle-income countries. (127) Little is known about the prevalence of stroke in diabetic patients in SSA, although early reports suggest it is low. For example, in a large study covering the period 1999-2012 in a major hospital in urban Cameroon, and involving 1688 patients admitted for stroke, the prevalence of diabetes was 12.8% (128) But there is likely wide variation depending on geographical setting

The special consideration of diabetes, TB, and HIV

Interactions between diabetes and infectious diseases are of particular relevance to SSA where the speed of epidemiological transition has been such that high rates of infectious disease coexist with a rising prevalence of NCDs such as diabetes. However, these interactions have been extensively reviewed elsewhere and comprehensive coverage of these areas are beyond the remit of the Commission. (129-132)

Clinical challenges of diabetes in SSA

The clinical challenges of dealing with diabetes in SSA are legion, yet despite differing levels of development and population structure, countries within the region face similar challenges concerning screening, diagnosis, and management. In this section we will consider issues of patient-proximate clinical relevance where common themes in the inability to provide quality care are lack of knowledge, lack of reliable access to medications, and lack of access to treatments for complications. Health systems will be discussed later.

Diagnosing diabetes in SSA

Poor awareness of diabetes, both at population and health care profession levels, means diagnosis is often delayed. For people with type 2 diabetes this delay will generally result in an unequivocally elevated random glucose at presentation. (6, 29, 133) Choice of the correct cut-off point or test to use for diagnosis of diabetes (panel 2) are therefore of less immediate relevance in the context of

routine clinical diagnosis and care, but whether or not the ADA guidelines (134, 135) for diagnosing diabetes apply to an African population will become increasingly important for the future as earlier detection of the condition becomes feasible. Presently, it is worth noting that although HbA1c is increasingly used as a diagnostic tool in Western countries, its use is likely to have challenges in Africa given that it relies on integrity of red blood cells, which can be affected by several conditions in SSA, for example haemolysis from malaria or sickle cell disease.

The ability to diagnose diabetes is complicated by the poor availability of diagnostic equipment in clinics, of laboratory facilities to process samples, and of transport between clinics and laboratory facilities. Rather than rely on the 'gold standard' measures put forward by the ADA, therefore, many practitioners rely on the use of capillary blood glucose measurements using point-of-care instruments, and urine strips. However, even these more 'simple' tests are often unavailable. For example, Beran et al found urine glucose strips were only available in 18% and blood glucose meters in 21% of health-care facilities in Mozambique. Blood glucose meters were available in 13% (urine glucose strips in 54%) of facilities in Mali and in 49% (urine glucose strips in 61%) in Zambia. (84, 136)

For people with type 1 diabetes a delay in diagnosis can prove fatal. Unfortunately, given that in low income countries the symptoms of type 1 diabetes - rapid weight loss, fatigue, abdominal pain, and confusion - can easily be confused, for example, with AIDS or cerebral malaria (137, 138), and that the condition is relatively rare, anecdotal reports and small studies suggest that presentation is often delayed. Indeed, Makani et al. found that 21 of 199 patients diagnosed as having cerebral malaria in Tanzania actually had diabetes.

Managing hyperglycaemia in SSA

Effective glucose control is essential for short term well-being and longer term protection from complications. Available evidence suggests that many people with diabetes in SSA fail to achieve adequate glycaemic control, although studies to specifically address this question have been relatively small. (139) (140, 141) Good glucose control is most likely to be achieved when there is reliable access to clinical services, availability of equipment to monitor control, when patients and health care professionals have good knowledge about diabetes management, and when efficacious and affordable treatment is available and is backed by adequate and effectively deployed measures of glucose control. In SSA, barriers are experienced at each of these steps. Manne and colleagues (7) found that only around a fifth of overweight or obese people at high risk of diabetes remembered ever being offered blood glucose testing, and just over a third of those who were identified as having diabetes remembered ever having a test done, and only a quarter were on treatment.

The ability to monitor control per se in SSA is difficult, even in a hospital setting. For example, in a survey of six countries done in 2011, only around 47% of patients with diabetes had had an HbA1C measured in the 12 months prior to the study; ranging from 27.5% to 81.1%. (122) In primary care settings, the situation is likely worse, however, we could not find any published data from SSA. Availability of other methods for measuring glycaemia in the clinical setting have previously been discussed. As discussed in panel 2, the choice of test to monitor long-term control is a key

consideration and although HbA1C is the test of choice in many centres in SSA. (29), whether this is the best test to use in an African population has not been adequately delineated. Other methods of monitoring control, for example, fructosamine or glycated albumin (16) may be more beneficial in populations for whom HbA1c is not reliable. These tests are not, however, widely available in SSA, and their potential value may need to be explored further.

Limited access to home blood glucose monitoring equipment in SSA impacts also adversely on patient education and empowerment which is a mainstay of diabetes management. (142) The median cost of a blood glucose strip in seven African nations was found to be $0.50 (range $0.20-$1.20), and the yearly cost of consumables for minimal reasonable care to families with a child or young person with diabetes in these countries ranged from 74-377% (median 126%) of per capita Gross National Income.(143)

The first step of diabetes treatment in HICs is lifestyle advice, but few patients with type 2 diabetes in SSA receive such advice. In addition, most people with type 2 diabetes require medication, with the most commonly available treatments being metformin and sulphonylureas, or insulin for those who fail treatment with these agents. Affordability should not - in principle - be an obstacle to treatment, since these medications are potentially available at an low cost, which is affordable to most, at either an institutional or personal level. Unfortunately, as wil be discussed later, supply-chain problems and price mark-ups are such that simple therapies may become unavailable or unaffordable at a patient level.

Newer and more expensive treatments are actively marketed in all parts of the world, (144) and may have advantages in certain subgroups of patients (145), but there are few outcome studies to show that they can achieve cost effective reductions in morbidity or mortality compared to the three basic medications. The pressing need, therefore, is to ensure that these basic medicines are available throughout Africa and that clinicians are well educated about the ability to treat diabetes with simple agents. (See Panel 1)

For type 1 diabetes the essential therapy is insulin. Unfortunately, insulin and other components of care are often either unavailable within the health care system or unaffordable to patients. These issues have been extensively reviewed by Ogle et al. (77) (figure 3) and Beran et al. (146) (figure 3). Safe insulin storage is also a problem for many families who do not have access to refrigeration and so clay pots are used for evaporative cooling. Encouragingly, evidence indicates that these methods are effective in reducing storage temperatures down towards room temperature (147). There are several non-governmental initiatives to provide care for people with type 1 diabetes, some of these are highlighted in appendix B. In addition to treating the disease, health care providers need to recognise that emotional impact on young people with T1DM and their families is often severe, especially in countries with relatively low health literacy (148). Knowledge can help to mitigate this burden and given the complexity of managing T1DM, diabetes education of the young person, their family, and health professionals, tailored to culture, language and education/knowledge levels, are critical in achieving good outcomes.

Management of co-existing risk factors

Overall CVD risk is logically addressed by treating overall risk rather than by focusing on hyperglycaemia alone. (149) See also panel 9. This approach presents challenges, but the Steno-2

study was a striking demonstration of the benefits of multifactorial intervention in type 2 diabetes (150) . Wherever possible, people with diabetes in SSA should have regular assessments of all CVD risk factors. However, studies reporting on such concomitant services in SSA have shown the difficulties of doing this. For example, in a slum in Nairobi, Werner et al found only 3.4% of people attended cardiovascular risk clinics on a regular basis during 34 months follow up (151). Although, the necessity for monthly attendance – which seems extreme, even by HIC standards - may have proven challenging for many. Adherence to recommended practice amongst medical professionals is also low, with many doctors in a cardiovascular risk clinic failing to follow guidelines for concomitant assessment of cardiovascular risk (152). Additionally, the guidelines for risk evaluation and reduction in diabetes in Africa are inconsistent, often focus on single risk factors, and are generally adaptations of guidelines from other settings. (153). More evidence from local settings is sorely needed to feed into local guidelines.

Although the Commission focused on diabetes and total CVD risk, we would be remiss if we did not mention that, given prevalence, the reduction of CVD in Africa requires a concerted effort to reduce hypertension per se. A recent systematic review of 33 surveys involving over 110, 000 participants in SSA found a pooled prevalence of hypertension of 30%, but only 27% of people with hypertension were aware of their status before the surveys, only 18% were on treatment and only 7% had acceptably controlled blood pressure. (154) In fact, the World Heart Federation puts tobacco and blood pressure control in third place in its nine steps to reduce global burden of CVD and does not mention control of hyperglycemia at all. (155) However, given that diabetes and hypertension often co-occur and interact synergistically, the increasing burden of diabetes that is likely to occur in SSA, and that the adverse effects of diabetes go beyond those of CVD, this important risk factor should not be marginalized.

Monitoring and managing complications of diabetes

Given the huge costs of managing complications of diabetes and the increasing burden of diabetes strategies to prevent complications are desperately needed in SSA. Adequate management of hyperglycaemia and other risk factors, and regular assessment for early evidence of complications are the cornerstones of successful strategies to prevent micro and macrovascular complications of diabetes. Diabetes registries, have been highly successful platforms to drive improved outcomes in these regards in high income countries, but issues with availability of technology and other necessary infrastructure, mean that these are largely absent in SSA.(81)

Availability of management strategies to prevent progression or treat complications of diabetes is generally poor in SSA. Challenges in preventing and manageing diabetic retinopathy and nephropathy illustrate the issues in SSA. Preventing and manageing diabetic retinopathy requires both good glycaemic control and the timely detection and treatment (with photocoagulation) of early stage sight threatening retinal changes. But there are insufficient ophthalmologists (about 1/1,000,000) or opticians to perform opportunistic screening for diabetic eye disease (156, 157). Non-physician cadres such as ophthalmic clinical officers receive relatively little training in retinal disease, and eye services are overwhelmed by other conditions. (158) The use of mobile digital photography with telemedicine links is a potential solution to deliver cost-effective, accessible screening to rural and remote populations and, given that fundus cameras remain prohibitively expensive (cost in the region of $15,000), validation studies are in progress for a number of portable fundus cameras.(159, 160). A simple risk score could be an attractive alternative, to select

those who are more likely to be diagnosed with retinopathy (or any other major complications) for transfer to screening and treatment hubs. However, fewer than 30% of countries have treatment facilities for retinal photocoagulation. (81)

The prognosis of diabetic nephropathy in Western societies has greatly improved over recent decades due to primary prevention (good glucose and blood pressure control) and secondary prevention (regular screening for proteinuria and ACE-inhibitor treatment following the onset of proteinuria). Furthermore, dialysis and renal transplantation have greatly extended the prognosis of patients with end-stage disease. (150) Unfortunately many patients with diabetic nephropathy in SSA may not have access to such treatments and often progress to end stage renal disease. (94, 161). In addition, many parts of SSA have no nephrologists at all (Kenya has one per 2 million population and South Africa just over one per million)[95] and dialysis is unaffordable to many patients(98). The average cost of renal replacement therapy is US $10-20,000 per year.

See appendix C for examples of successful initiatives for diabetic retinopathy and the diabetic foot.

Screening and prevention of type 2 diabetes

All commissioners are agreed that the best way to manage the diabetes epidemic facing SSA is by preventing the change in dietary habits and decline in physical activity leading to overweight and obesity that are pervasive across the continent. The social, economic, cultural, and political elements that are needed to ensure that this is achieved is far beyond the remit of this Commission, however, and readers are referred to other extensive literature on this subject, as summarized in the Lancet Obesity and Physical activity series. (162)

Evidence indicates that screening for diabetes in high-income countries is not beneficial (77). In addition, no evidence from LMICs suggests that screening would be a valuable approach to successfully identify and manage people with diabetes or hypertension (163). Nevertheless, given the massive number of people in SSA who have diabetes and go undiagnosed, many academics and policymakers maintain that targeted screening should be employed to enable earlier identification and treatment. (164) Whether such targeted screening will work in practice in LMICs, the risk scores that would be effective for selecting patients to screen, what level of health system infrastructure will need to be put in place to enable it, and the cost:benefits of instigating such screening, is currently unknown and research is urgently needed to answer these questions before potentially costly screening programs are put in place without knowledge of their utility. It has also been suggested that platforms for detecting communicable diseases could be co-opted to screen for diabetes and cardiovascular risk factors. Again, there is no evidence that this will be a cost effective method for improving outcomes and research in this area is needed [JD, Geldsetter in press TLDE].

<u>The next steps</u>

The factors limiting access to prevention and management options for diabetes, its fellow cardiovascular risk factors, and complications in SSA are similar. These are: poor understanding of diabetes and its complications among healthcare professionals and patients, delays in seeking

medical attention, delays in patient referral for specialist care, poor diabetes - and other risk factor - control, inability of patients to afford treatment or afford transport to attend treatment facilities, and - in some cases - a preference by patients for alternative traditional therapies in the first instance.

Throughout this section we have illustrated the difficulties in receiving good care for the diabetic patient in SSA. We have also given some examples of the success seen in HIC countries, but whether or not these are transferable to SSA requires future research. Additionally, diabetes affects multiple physiological systems and interacts with many other diseases to increase the risk of adverse outcomes for a patient. It is clear, therefore, that broad based health system improvement strategy is central to improving outcomes in diabetes. In the following parts of the report we will move from clinical – patient proximal - considerations to considering health systems approaches necessary to support clinical aims.

Health system responses to diabetes in SSA

Although health systems are pivotal in a successful response to diabetes, the majority of research on diabetes in SSA has generally focused on epidemiology and clinical presentation, with few studies that explored health systems, but these studies were limited in scale and scope.(81, 165)

We used published studies and analysis of surveys to explore health system responses to the rising burden of diabetes in SSA. We used an established health systems framework to guide our analysis and systematically examined response to diabetes in key health systems functions of organization and governance, financing, resource management, and service delivery (166).

Organization and governance of diabetes in health systems of SSA

The state capacity, organizational and governance structures, and institutional strength of health systems vary across SSA. In 2010, 42 countries of SSA had reported having a unit or department within their ministries of health with responsibility for NCDs (167), but just seven countries had a national operational policy, strategy, or plan for diabe This situation has ostensibly improved, and in 2015, the WHO report on Assessing National Capacity for the Prevention and Control of NCDs (81) stated that 93% of countries in the WHO Africa region have a "unit, branch, or department" in their ministry of health that is responsible for NCDs and 72% of countries had an "operational policy, strategy or action plan" for diabetes. However, looking specifically at SSA (167, 168) only 20 countries had an operational policy, strategy or action plan for diabetes, 9 did not, and the remainder did not respond.

In 2010, the availability and the stage of implementation of guidelines, protocols, or standards for diabetes management varied across countries. Just four countries in SSA had guidelines, protocols or standards that were fully implemented(81) . Although data are not available specifically for SSA, in 2015, globally, 75% of countries reported guidelines for dealing with diabetes(81), hence the situation is likely to have improved in the region since 2010.

Financing of diabetes in SSA

In 2014, total health expenditure in SSA as a proportion of GDP averaged 5.5% (ranging from 6.4%

in the 23 low income countries, 6.0% in the three low middle-income countries and 5.4% in the five upper middle-income countries and 3.3% in one high income country).(3, 8) 19 countries were below the Chatham House recommendations of 5% of GDP spend on health.(169) In the same year, average public spending on health accounted for 42.6% of total health spending.(3, 8) External funding ranged between 64.9% in the Gambia to 0.3% in Equatorial Guinea, with an average of 11.2%.

In 2001, African nations adopted the Abuja Declaration, pledging to allocate at least 15% of their national annual budgets to health spending.(170) Yet, by 2013 only seven countries in sub-Saharan Arica – the Central African Republic, Ethiopia, Malawi, Rwanda, Swaziland, Togo and Uganda – had reached that target.

In 2014, the average level of out of pocket expenditures as a proportion of total expenditures on health was 34.5%, ranging from 73.5% in Sierra Leone to 2.3% in the Seychelles. (3, 8, 168) In 7 countries, out-of-pocket expenditure comprised more than 50% of total health expenditure (down from 12 countries in 2010). Although unknown, we assume out-of-pocket expenditures are likely to be high for diabetes, and will often be prohibitive, producing financial barriers to access and leading to many diabetic individuals not seeking care (and thus avoiding short-term treatment costs but potentially accumulating larger health deficits which lead to even higher long-term direct costs through more severe sequelae due to target organ damage, such as amputations, blindness, stroke or kidney failure, in addition to shorter life span). Co-morbidities and sequelae in many instances result in 'catastrophic' or 'impoverishing' healthcare expenditures, sinking many patients and their families beneath the poverty line. For example, in a multi-country study that included Tanzania catastrophic expenditures with cardiovascular events in low-income population groups were reported to be 92%, with distress financing ranging from 4% to 12% in low-income groups. (171)

Low levels of public funding, low income levels and high out-of-pocket expenditures have adversely affected the uptake and provision of care for diabetes patients, increasing the likelihood of long-term complications. In Malawi, for example, families spent 22% of their monthly per capita budget on out-of-pocket expenditures related to NCDs.(172, 173) For patients with type 1-diabetes high out of expenditures have and unaffordability of care has grave

consequences, with high mortality levels among patients, as regular insulin injections are not always affordable.(25, 146)

To increase health financing for NCDs, several countries such as Cameroon, Botswana and Seychelles, have introduced earmarked taxation to influence health behaviours, with revenues channelled to health promotion activities. Others have launched reforms to increase public funding for health systems and to achieve universal health coverage, but large informal sectors hinder effective tax collection to invest in health systems.(174)

Resource management in health systems for tackling diabetes in SSA

Sub-Saharan Africa has an acute shortage of healthcare professionals: the WHO African Region accounts for 25% of the current global health workforce shortage, expected to rise to 34% by 2035 as a result of population growth in Africa.(175) The shortage of health workers, exacerbated by emigration (176) , has constrained the achievement of the Millennium Development Goals in SSA.(177)

There is shortage of medical graduates (more than half of the countries in SSA have only one medical school, and 11 countries have no medical school)(175, 176) and nurses, whose level of training and skills vary greatly across countries (178). More than one half of SSA countries have a category of non-physician clinician (providers who complete an average of about three-years of post-secondary clinical training) (178) and many countries such as Ethiopia and Malawi have successfully used community health workers (CHW) to scale up HIV, tuberculosis, malaria and other essential services.(179, 180)

The lack of human resources affects the capacity of health systems and their readiness to manage diabetes is revealed by examining WHO Service Availability and Readiness Assessment (SARA) (181) survey in eight SSA countries (Benin 2013, Burkina Faso 2012 and 2014, Democratic Republic of Congo 2014, Kenya 2013, Mauritania 2013, Togo 2012, Uganda 2013, Tanzania 2012, Sierra Leone 2012, and Zambia 2010). WHO SARA surveys are designed to assess national capacity of health systems in countries and can be applied to assess prevention and control of NCDs, by measuring the availability of diagnostic tools, essential medications and trained staff at

the facility level using tracer conditions such as diabetes and cardiovascular disease.(182)' The methodology for the surveys is described elsewhere. The findings from the country-level SARA reports indicate that there are major gaps in front-line service delivery. In the eight study countries, less than one half of facilities offered diabetes management. Of the facilities not offering diabetes services at the time of the survey, just 40-60% demonstrated service readiness (Table 2).

Table 2

With the exception of Uganda, only about one-third of facilities offering diabetes services had guidelines for treatment, and one-third or fewer had at least one trained staff. The discrepancy between trained staff and availability of diagnostic supplies and medication is concerning as it is not clear how supplies and medications are being used in the absence of staff with formal training in diabetes care. The availability of blood glucose testing ranged from 14% in Burkina Faso (which is similar to what Beran et al found in Mali and Mozambique (183) to 80% in Uganda – although only 31% of Uganda sites reported the availability of trained staff.

The examination of reports of SARA surveys add to the findings of the literature reviews done in the clinical system to lay bare the consequences of underfunded and weak health systems and years of suboptimal investments in human resources (184), which have led to large resource gaps for diabetes care in SSA.

Availability and access to medicines for diabetes in SSA

According to WHO, in 2010, essential medicines for diabetes were not available in all SSA countries: out of the 45 countries surveyed, oral medicines such as metformin and glibenclamide are available in 29 and 35 countries respectively, insulin in 32 countries and aspirin (acetyl salicylic acid – ASA 100) tablets used for primary prevention of cardiovascular disease in patients with diabetes was available in 41 countries (168). In 2015, however, the WHO assessed that in the 47 countries in the WHO Africa region, 51%, 40%, and 71% countries had availability of metformin, insulin, and aspirin in the public sector (81), respectively.

The WHO Global Action Plan (GAP) for the Prevention and Control of NCDs 2013-2020 (185) has a target of 80% availability for affordable basic technologies and essential medicines, including generic drugs, required to treat major NCDs in both public and private facilities. While reaching this target is essential if SSA countries are to meet the 25% relative reduction in premature mortality from NCDs by 2025, studies reveal access challenges, due to a lack of availability and affordability of medications. For example, studies reveal 75% median availability of insulin in the public sector of (5 countries) and 46% in the private sector (6 countries) (146), and challenges to availability and affordability of oral medicines.(136, 186-188) In 2004-2013, just 16.7% of the SSA countries bought insulin every year and 29.2% of countries did not buy insulin.(189)

WHO SARA survey reports on the nationwide availability of insulin, metformin and glibenclamide for nine SSA countries reveal that median availability of insulin was 13% (range: 3%-39%), and decreased at lower levels of the health system, with 12% median availability in rural areas and 7% in urban areas, and 11% in the private sector and 9% in the public sector. The median availability of metformin was 22%, (range: 2% to 57%), with decreasing availability at lower levels of the health system and higher availability in rural areas and the private sector. The findings were similar for glibenclamide which was more available in urban areas.(181) These data are presented in Table 3.

Table 3

These medications are not expensive, however. Data from Management Sciences for Health (MSH) provide international reference prices for many medicines.(190) The prices quoted by MSH are from tenders of ministries of health, and represent medicine prices without any add-on costs at the point of entry to a given country. Analysis of data from 1996 to 2013 suggests that the median price for insulin (10ml 100IU/ml vial) in SSA (8 countries) was $7.15 (range: $1.52-17.58) at constant 2015 prices.(191) For metformin (500mg; 10 countries), gliclazide (80mg; 4 countries) and glibenclamide (5mg; 13 countries) the median prices were $0.018 (range: $ 0.002-3.304), $0.023 (range: $0.012-0.060) and $0.004 (range: $0.0004-0.032) respectively. The treatment costs, using Defined Daily Dosage (DDD) (192), are presented in Table 4.

Table 4

Table 4 shows that treatment with insulin presents a significantly higher cost for individuals compared to oral medicines for diabetes. In addition to purchase price, medicine costs are influenced by the cost of delivering medicines and mark ups along the supply chain. (146) The prices presented in Table 4 do not take into account of mark-ups, such as value added sales tax, local taxes, international purchasing verification tax, insurance, defence levy, overheads mark-up, bank fees, fee for import declaration form, port clearance, importer margin, handling cost, wholesale mark-up, retail mark-up, health facility mark-up, dispensing charge or other mark-ups within the system. They also don't reflect the additional costs of ensuring adequately trained health care personnel to prescribe the treatments. Although data are lacking for these mark-ups, specifically for insulin, for other medicines the additional cost of these taxes and levies have been found to range from 18.4% to 94.4% of the final retail price of the medicine.(191)

These add-on costs as well as subsidies within health systems mean that there are many factors influencing the price and affordability of insulin and total cost of insulin needs can vary from 0.2% of total GDP in South Africa to 13.4% in Malawi.(191) For example, data from four studies undertaken in three African countries at different times suggest that in Mozambique (2003) and Mali (2004) there was an increase in medicine prices between the central government and health facilities to recuperate storage and transportation costs. An increase in prices was not observed in Zambia and Mozambique (2009).(183) In Mozambique and in Zambia the price between the facility and the patient was subsidised, whereas in Mali there was an additional mark-up, such that there was a 47% increase between the government purchase price and patient purchase price. In order to present different prices of insulin we combined different data sources to show the median price (at 2015 prices) at different levels of the health system [ACCISS Study. Price survey of insulin. Amsterdam: Addressing the Challenge and Constraints of Insulin Sources and Supply Study, in press](Figure 4).

Figure 4

Figure 4 shows that comparing the MSH prices to those obtained by different ministries of health many countries were purchasing insulin at the best price possible, but there were outliers. In some countries, insulin was provided free or subsidised or patients in the public sector, whereas

in others the prices were higher, but still relatively low in comparison to prices in the private sector. The prices presented in Figure 5 are not affordable to individuals in some countries, for example $10.88 in the public sector in Mali or $50.57 in the private sector in Ethiopia. (191)

Data from WHO/HAI suggest that in some SSA countries people had to pay between 0.9 to 6.7 days of wages to pay for their diabetes treatment (Figure 6).(188) Affordability is defined by WHO/HAI as the lowest paid government worker paying only one-day's wage for treatment. Hence, according to the data presented in Figure 5 suggests only glibenclamide in Ethiopia is affordable.

Figure 6

However, in SSA many individuals do not work in the formal sector, and hence measuring affordability in terms of the wage of the lowest paid government worker is problematic, especially as most people live on less than $1.90-3.10 per day.(193) A comparison of annual cost of diabetes medicines (Table 4) and daily costs of the different diabetes treatments, using different poverty thresholds of daily income, shows that daily drug costs (ministry of health purchase prices and not retail price) represent 0.5-15.1% of income for someone living on $1.90 per day (Table 4).

Health service delivery for diabetes in SSA: analysis of Service Delivery Indicator Surveys

To elicit service delivery gaps in diabetes care we analysed data from Service Delivery Indicator (SDI) surveys conducted in six SSA countries by the World Bank, in cooperation with the African Economic Research Consortium, and the African Development Bank.(194)

The SDI surveys include primary health facility level data on expenditures, provider effort (absence rate, caseload per provider), provider knowledge and ability (diagnostic accuracy, adherence to clinical guidelines, and management of maternal and neonatal complications), and inputs (availability of supplies, equipment, and drugs). Diagnostic accuracy is measured through patient case simulations (vignettes) for the following seven tracers: (i) malaria with anaemia; (ii) diarrhoea with severe dehydration; (iii) pneumonia; (iv) diabetes; (v) pulmonary tuberculosis; (vi)

postpartum haemorrhage; and (vii) neonatal asphyxia.

The SDI surveys are complementary to and build on surveys (e.g. WHO SARA surveys) that focus on the availability of resources and health system readiness for service provision, including NCDs. Our analysis of SDI surveys broaden and deepen our understanding of service delivery and the quality of diabetes care by providing insights into the knowledge, ability and effort of providers (technical quality) and the availability of important inputs, such as drugs, equipment and infrastructure (structural quality). See appendix G for more information.

We investigated the four publicly available SDI surveys: Kenya (2012), Nigeria (2013), Tanzania (2014), and Uganda (2013).

We provide a summary of the provider and facility characteristics in Table 5. The total sample consisted of 6,139 providers, with the largest number of providers in the sample coming from Nigeria. With the exception of Tanzania, nurses, midwives, and community health workers represented more than half of the sampled providers. In Tanzania, 74% of the sample consisted of physicians, medical or clinical officers. In Nigeria, physicians represented only 9% of the sample, while nurses, midwives, and community health workers represented 81% (largely community health workers). In Kenya, Nigeria and Uganda, the majority of sampled providers were female.

Facility statistics in Table 5 shows that higher shares of providers in all countries were employed at lower level facilities (dispensaries/health clinics or health centres) and were primarily located in rural areas. On average, providers worked at facilities with a high equipment index, suggesting that they had access to a thermometer, adult weighing scale, sphygmomanometer, and stethoscope. In Nigeria and Uganda, however, more than a third of providers did not have access to all four pieces of equipment.

Table 5

When presented with vignettes, less than 50% of the sampled providers in all countries were able to accurately diagnose diabetes, with the exception of Kenya where 82% of providers gave the

correct diagnosis (weighted results). As shown in Figure 6, compared to other tracer conditions simulated in the vignettes, diabetes was the second least diagnosed condition (after diarrhoea with severe dehydration). Conversely, more than 80% of providers were able to diagnose tuberculosis and neonatal asphyxia, with the share as high as 97% and 91% in Kenya and Tanzania, respectively. Only 4% of the sample was able to diagnose all seven conditions. The share was highest in Kenya, where almost 17% of the surveyed providers correctly diagnosed all conditions presented during the patient simulation.

Figure 6

While the average clinical guideline score was less than 30%, indicating the degree of adherence to diabetes clinical guidelines, we observed a wide range of performance scores with some providers performing all the necessary tasks in the domains (symptom, patient, history, and physical examination) of the score (Figure 7).

Figure 7

The majority of providers who correctly diagnosed diabetes could not prescribe the appropriate treatment and indicated that they would refer the patient for a follow up visit at a specialist diabetic clinic or higher level facility for initiation of treatment (Figure 8). In Tanzania, however, 89% of providers indicated that they would prescribe oral hypoglycaemics and 49% would refer patients to more specialized facilities. Whether this pattern of referring-on is due to lack of knowledge or lack of confidence in applying the knowledge is not known, however, as numbers of diagnosed patients increases referring the majority to higher level facilities in unlikely to be a sustainable option.

Figure 8

In Table 6 we present the logistic regression results of the factors associated with a provider's ability to diagnose diabetes. Female providers had significantly lower odds of correctly diagnosing diabetes in Kenya (0.57 OR; 0.34 - 0.94 95% CI) and Nigeria (0.73 OR; 0.62 - 0.87 95% CI), but we

cannot explain the reasons behind this. Relative to the highest cadre category (physicians, medical or clinical officers), lower cadres had significantly lower odds of diagnosing diabetes in all countries. This result suggests that there is room for improvement in training lower cadres of health providers to deal with diabetes.

Table 6

It is encouraging that geographical location was only a significant predictor in Nigeria, with providers in rural areas having lower odds of diagnosing diabetes than those in urban areas. We did not find a statistically significant relationship between the ability of providers to diagnose diabetes and whether the facility was public (Table 6). Interestingly, in all four countries, a higher equipment index (score created from availability of a sphygmomanometer, adult weighing scale, thermometer, and stethoscope) was found to significantly increase the odds of correctly diagnosing diabetes.Although availability of a glucometer was not generally recorded in the SDI surveys, good availability of other equipment may be reflective of the availability of a glucometer and hence increase the ability to diagnose diabetes. As mentioned earlier, the variation in the equipment index was quite low with the majority of providers having access to the basic equipment (particularly in Kenya), thus the significant odds ratios suggest that ensuring universal availability of basic equipment could substantially improve diagnostic accuracy.

In table 7 we present the OLS regression results of the factors associated with higher clinical guideline scores. The dependent variable is the log transformed clinical guideline score. The results are consistent with the findings related to diagnostic accuracy. Lower cadre providers are less likely to have higher clinical guideline scores. Nurses, midwives, and community health workers are found to have 5-7% lower clinical guideline score than physicians, medical and clinical officers. In Nigeria and Tanzania, providers at district hospitals are found to have a 7 % higher clinical guideline score than providers at the lowest level facilities. The equipment index is also positively associated with the clinical guideline score in all four countries.

Table 7

The analysis of service delivery indicators suggest that in the countries studied, there is low

readiness across all levels of care and for all cadres of health professionals in management diabetes for correct diagnosis, adherence to guidelines of care and in providing appropriate treatment. Even the majority of providers who correctly diagnosed diabetes could not prescribe the appropriate treatment and indicated that they would refer to higher levels. In particular, lower levels of care are unprepared for diagnosis and treatment of diabetes, which has implications for developing and scaling up a community- or primary health care based diabetes management programmes in sub-Saharan Africa.

Health system responsiveness to diabetes in SSA: implications

The examination of the reports from WHO SARA surveys, and the analysis of World Bank Service Delivery Indicator surveys revealed health systems unprepared for delivering effective health services for diabetes patients. However, a comprehensive understanding of how resource and service gaps in health systems affect demand, and how the interaction of supply-side gaps and demand-side dynamics translate to unmet need in SSA is constrained by lack of data. We provide in the next section a new analysis of surveys in 10 SSA countries to examine the nature and extent of unmet need at each critical stage of the diabetes care process.

Analysis of Cascade of Care and Unmet Need for diabetes in SSA

One innovative analytic approach for assessing health system performance is the construction of a cascade of care using a tracer condition. The cascade of care analysis involves quantitative depiction of the step-wise care for the population affected by a disease of interest, including screening, diagnosis, linkage to treatment programmes, adherence to treatment and finally achievement and maintenance of control. It depicts the dynamics between demand and health system responses at each step of the care continuum and provides the opportunity to identify areas of unmet need and where attrition in care occurs.(7)

Cascade of care analysis has been used to monitor progress toward coverage goals for populations affected by HIV/AIDS.(195, 196) In the United States, 2007-12 data from the National Health and Nutrition Examination Survey (NHANES) have been used to construct cascade of care for diabetes to show that nearly one third of patients with diabetes were unaware of their diagnosis and the undiagnosed were less likely to achieve health targets for multiple chronic

diseases.(197)

We used individual-level data from population-based surveys undertaken in 2005 and 2013 in 10 selected SSA countries that included diabetes to assess cascade of care for diabetes. The WHO STEPS Survey was available for 8 countries. The STEPS Survey is a standardised approach to collecting data about NCDs among adults aged 25-64 years in WHO member countries. In brief, the STEPS Surveys include collection of demographic data (STEP 1), physical measurements such as blood pressure and BMI (STEP 2) as well as biochemical measurements, including fasting plasma glucose (STEP 3).(198) Further details about the STEPS instrument are provided elsewhere.(18) Given that a standardised approach is used across all countries, data from the STEPS Surveys can be used to compare epidemiology and health system performance across countries. STEPS Survey data were available for the following countries: Benin, Comoros, Guinea, Liberia, Mozambique, Seychelles, Tanzania and Togo.

We supplemented the data from the eight STEPS with information from the Demographic and Health Survey for Namibia (2013), which as with STEPS surveys includes both fasting plasma glucose measurement and self-reported data on access to diagnosis and treatment for diabetes.(199) For South Africa, we utilized the South Africa Nutrition and Health Examination Survey (SANHANES), a nationally representative cross-sectional health and nutrition study led by the South African Human Sciences Research Council.(200) Together, the STEPS, DHS and SANHANES surveys represented 39,062 individuals across 10 countries over the period from 2004-2014. The methods have been described elsewhere.(7) We also present in appendix A how we pooled individual data from different data sets to enable comparability. In Panel 7 we describe the approach used to define diabetes and the way we constructed the care cascade.

Panel 7: Definitions and constructing the diabetes care cascade

Diabetes was defined based on the current WHO and American Diabetes Association diagnostic criteria as any one of the following: a fasting plasma glucose greater than or equal to 7.0 mmol/l (126mg/dl); a 2–hour plasma glucose ≥ 11.1mmol/l (200mg/dl) or; a HbA1c measurement ≥ 6.5%.(134, 135) This definition represents the current gold-standard clinical practice guidelines that are being used internationally. The data had one or more of these measures (see appendix

A) and hence there may be underreporting

Those reporting use of medication for diabetes were also classified as diabetic irrespective of the biomarker values. Respondents who self-reported a diagnosis of diabetes, but were not on medication and lacked the criteria indicated above were not classified as diabetic. In addition, we quantified met need for four different metrics of diabetes care in the diabetic population: ever receiving a blood glucose measurement as a measure of diagnosis; ever having been told about the diagnosis of diabetes as a measure of awareness of diagnosis; receipt of any advice from a healthcare provider to lose weight or exercise (hereafter "any advice') and use of either oral medications or insulin, for treating diabetes (hereafter "any medication").

Using these metrics, we constructed a diabetes care cascade for each of the 10 countries. This cascade, created using individual data, shows the percentage of the total diabetic population that self-reported reaching each subsequent step in the care process, conditional on having reached the previous step.

First, we identified those ever having had a blood glucose measurement (prior to the STEPS or other Survey on which the diagnosis was made) as an indicator of having had an appropriate diagnostic test for diabetes.

The second, among those who had received a blood glucose measurement, we then quantified the percentage of all diabetic patients who had been informed about their diabetes diagnosis by any healthcare provider as a measure of awareness of diagnosis.

Third, among those who had received a diagnostic test and were aware of their diagnosis, we calculated the percentage of the total diabetic population who then received any advice regarding lifestyle modification and finally, among that group, the percentage that had received oral medications or insulin for diabetes control.

The methodology used to merge data from different surveys, the construction of the care cascade and the analysis to identify unmet need, and also the limitations of the analysis are described in detail elsewhere. (7)

The diabetes care cascade in the combined countries is displayed in Figure 9. The first step in the cascade is receipt of a diagnostic test, specifically a blood glucose measurement. This initial diagnostic test was associated with the largest loss to care across all countries, with an average of 40% and ranging from 23% to 81%.

Figure 9

Second, among the group who self-reported having received glucose measurement, the cascade shows that on average 18% of the total diabetic population was then lost to follow-up at the stage of being told about their diagnosis by a healthcare provider, with a range of 0% to 26% (Figure 9).

Third, among those who reported completing the first two steps in the cascade, figure 14 shows that an additional 16% of the total diabetic population was lost to care and follow up at the stage of receiving advice on lifestyle modification, with a range of 5% to 15%.

Fourth, a further 2% was lost to care between the stages of receiving advice and receiving any medication treatment (range 3% to 10%), including oral medication or insulin, for diabetes control. Overall the analysis of the data from the 10 surveys shows that the percentage of the diabetic population who completed the care cascade in different countries averaged 24% with a range of from 9% to 58%. (Figure 9)

The pattern of care cascade by country varied widely. For instance, in Benin there was a very rapid drop in the first step with 60% of patients with diabetes not having their glucose measured. Thereafter, there was a steady decline with a 14-percentage point decline from patients who were aware of diagnosis to receiving advice. Overall, just 22% of the patients with diabetes received medicines. In Comoros, there was steady decline at each step with 33% of patients received advice and medication overall. In Guinea, which has a weak health system and has been affected by the Ebola virus outbreak, there was a sharp drop at the first step, with just 40% of patients with diabetes having glucose measured. A steady decline after each step thereafter meant that overall just 20% of diabetes patients received advice and 17% received medication.

Comment [TB1]:

The pattern of cascade in Liberia, a country with a weak health system affected by the Ebola virus outbreak, mirrored that in Guinea, but decline at the first step was greater. Only 19% of patients with diabetes had their glucose measured and overall the proportion of patients receiving advice and medication was 8%. In Mozambique, the pattern was similar to that observed in Benin and Guinea, with a sharp drop at the first step in the care cascade by 69% so that only 31% of diabetic patients had their blood glucose measured followed by a steady attrition in the care cascade, which meant that just 19% of patients received medication.

Namibia had the best profile of diabetes care cascade among the 10 countries studied, with a less sharper decline of 39% at the first step, with 61% of patients with diabetes having their glucose measured. The declines at each step thereafter were less marked such that 39% of patients with diabetes received advice and 36% received medication. The cascade pattern in Seychelles, which has one of the highest prevalence rates of diabetes in SSA, was different to the rest of the study countries. While around 92% diabetic patients had their blood glucose levels measured, there was a sharp decline at step two with a fall of 52 percentage points, so that just 40% of patients were aware of their diagnosis and 24% were receiving medication. In South Africa, the pattern of cascade of care mirrored that of Namibia, but the lost to follow-up at each step was greater than that observed in Namibia, so that 29% of patients were able to receive advice and 26% receive medication. In Tanzania, 50% of patients had their glucose measured, and almost all of those receiving a glucose test were aware of their diagnosis (49%), with 34% of patients with diabetes receiving advice and 29% receiving medication. Togo had the least favourable profile, along with Guinea and Liberia, with a sharp drop at the first step, with 29% of patients receiving a test to measure their glucose levels. There was a decline at each step so that just 9% of patients received advice and only 7% received medicines.

The care cascade for each of the 10 countries is shown in appendix D. The analysis shows unmet need at every step of the diabetes care continuum that leaves the largest proportion of patients going undiagnosed. For those diagnosed with diabetes, health systems are not able to provide services needed, with the majority of the patients with diabetes not receiving advice and the medication they need. Unmet need and suboptimal care means that patients will likely have delayed presentation to the health system and receive advice and medication late in the care process, with adverse effect on health outcomes which produce difficulties for patients and their

families due to ill health, with adverse economic consequences for patients, their families and the country at large.

We present in the next section our estimates on the economic consequences of diabetes in SSA.

Economic consequences of diabetes in SSA

Beyond ill health and lowering quality of life substantially, diabetes mellitus imposes a non-negligible financial burden on affected individuals, families and societies. While patients with diabetes face direct costs of illness through medical treatment of the disease, its comorbidities and sequelae, they also experience income losses through reduced productivity and disability, which in severe cases means inability to work.

Economic burden of diabetes to individuals

The relatively high prices for necessary health items such as blood glucose strips and insulin impose considerable financial burden on individuals as discussed in previous sections of this report. Combined with the substantial reliance of health systems in SSA on out-of-pocket expenditure, diabetics in SSA often have only limited access to adequate and timely treatment potentially resulting in an increased risk of diabetes-related health complications. Moreover, co-morbidities and target organ damage due to diabetes might cause catastrophic healthcare expenditures, shifting many patients and their families beneath the poverty line. (201) Simultaneously, these adverse effects are likely to be perpetuated in absence of adequate social security systems, where families may attempt to offset such catastrophic expenditures by shifting children into workforce, thus effectively bereaving them of any future prospects of financial wellbeing.

The measurement the of direct economic burden to individuals is complicated by the fact that health expenditure for diabetes-related complications are difficult to quantify since diabetes may not be the only attributable cause. The International Diabetes Federation therefore derives estimates for direct costs of diabetes from each country's total health expenditure applying age- and sex-specific ratios of average heath expenditure for diabetics and non-diabetics. Accordingly, estimated average per patient expenditures in 2015 in SSA for diabetes range between $243 and $419 (15), but the validity of these numbers is unknown as cost ratios were based on US data. A recent study using a similar approach but different cost ratios for LMICs found average per patient costs of $580.(202) Other studies estimated direct cost of diabetes per person per year to be $138 in Tanzania in 1989/1990 (203), and $489 in Cameroon in 2001 (204) . While not all of these expenditure are borne by individuals directly through out-of-pocket payments, increased insurance contributions and taxes additionally burden individuals.

Indirect costs of illness results from productivity losses of workers during their productive years (as costs of early mortality are not borne by diseased individuals themselves we do not consider this position in this section). These productivity losses comprise absenteeism (sick workers failing to

appear for work), presenteeism (unfit workers coming into work where they are unable to perform to full capacity), and labour-force drop-out (Panel 8). Notably, while in high-income-country productivity losses may be partially or fully offset by social security systems (e.g. continued pay during sick leave, insurance payments in case of permanent disability), in SSA they are likely to fully accrue at the level of sick individuals through foregone wages from formal or informal work as well as reduced agricultural yield in the case of subsistence farmers.

Panel 8: Labour-market effects of diabetes

Based on a systematic review and assessment of the currently available empirical evidence on the labour-market effects of diabetes, a recent global cost-of-illness study estimates that the drop in labour force participation of diabetic individuals in high-income countries (HICs) is 12.6% for men and 25.2% for women, while in low-and middle-income countries (LMICs) it ranges from 1.1% to 13.2% for men and from 1.2% to 17.4% for women (202). Moreover, in high-income settings, male and female diabetics who are in the labour force are found to be absent from work for 1.9 to 4.3 additional days a year, while the corresponding numbers in LMICs range from 1.9 to 8.6 excess days for men and 2.8 to 10.2 excess days for women. Finally, diabetic workers' productivity losses while at work (presenteeism) are found to be 0.3% in HICs and vary between 0.6% and 1.0% in LMICs.

The underlying empirical evidence largely draws on data from high-income and upper-middle income countries. Effects on labour market drop out as well as presenteeism are based on studies from the US (205, 206) and Mexico (207, 208). Although the diversity of sources is larger for absenteeism, with studies from the US (209), Mexico (208), India (210), Iran (211), and Namibia (212), it is unclear to which extent these labour-market effects accurately capture the situation in SSA. For instance, the combination of limited capabilities for blood sugar levels management and a shortage of preventive treatment is likely to lead to high rates of severe complications in the long-run, hence potentially increasing the rate of labour force drop-out.

Economic burden of diabetes to countries

Evidence on the total economic burden of diabetes to societies in SSA is rare. Kirigia et al. (213) estimated that the combined direct and indirect costs amount to Int-$ 25.51 billion (PPP) in 2000, but they may not have captured the full picture as diabetes-related complication were excluded from their analysis. This Commission therefore bases its evaluation of economic burden to countries on a top-down approach used in a recent study by Bommer et al. (202). Analysing direct health expenditure and indirect costs of diabetes, they estimated the global economic burden in adults in 2015 to be $1.31 Trillion or equal to 1.8% of world GDP.

Comment [CB2]: Kirigia JM, Sambo HB, Sambo LG, Barry SP. Economic Burden of Diabetes Mellitus in the WHO African Region. BMC International Health and Human Rights 2009; 9:6. doi:10.1186/1472-698X-9-6

Using prevalence and mortality data from the IDF Diabetes Atlas (15), the study estimated direct costs based on countries' per capita health expenditure assuming literature-derived ratios between the age- and sex-specific treatment costs for diabetic and non-diabetic individuals. These

ratios vary between HICs and LMICs, women and men within HICs, rural and urban areas within LMICs as well as between diagnosed and undiagnosed diabetics, thus extending previous work by the International Diabetes Federation. Note, however that no appropriate studies for SSA could be identified such that the applied cost ratios may not fully reflect the situation in the region. Indirect costs were defined as productivity losses due to mortality or disability, as measured by forgone labour earnings. As the wage data from SSA countries are scarce, labour earnings were proxied by the labour income share in GDP per working age person as measured in 2015 US$. A more detailed discussion of the methodology is provided in Bommer et al. (202) and in appendix E.

Based on the same approach and using national account data from the World Development Indicators database (8) for 47 sub-Saharan countries, we estimated the overall costs of diabetes in 2015 for SSA to $19.45 billion or 1.2% of cumulative GDP of the whole of SSA. Around 44.4% of this burden ($8.64 billion) arose from indirect costs. About $12.10 billion of the $19.45 billion (62.2%) occurred in Southern Africa, mainly in the relatively wealthy South Africa, and only $1.70 billion (8.7%) in Western Africa. The share of indirect costs by region varies from 23.2.2% to 49.2% (figure 10).

Figure 10

Productivity losses consisted of four components: (i) premature mortality (which amounted for 91.0% of total indirect costs ($7.86 billion)), as dead individuals are permanently unavailable to the labour market (ii) diabetes-related complications and malaise, which make diabetic patients less likely to participate in the work force (“drop out” accounting for 6.2% of total indirect costs ($0.53 billion)) (iii) more likely to take sick leave (“absenteeism”, accounting for 1.9% ($0.17 billion)) and (iv) decrease their productivity while working (“presenteeism”, which amounted to 0.9% ($0.79% ($0.07 billion)) (Figure 11). These estimates provide important benchmarks for the economic value that could be generated through improvements in initiatives to address diabetes risk factors, diabetes prevention, and early diabetes diagnoses.

Figure 11

An important question for policy makers in SSA is how the economic costs of diabetes are going to evolve in the short- and medium-term. To investigate this, we follow previous projection attempts of the International Diabetes Federation (15) by using quinquennial United Nations Population Prospects data for the years 2015 – 2030 (using the medium variant provided by the UN Population Division) (214), as well as projected urbanization rates projected by the UN (215) when estimating our projections of economic cost. Both demographic changes and urbanization rates are likely to be substantial drivers of future costs as an urban sedentary lifestyle is considered an important risk factor for diabetes (216). Our projected economic costs also take into consideration real GDP and GDP per capita growth (extrapolated based on past growth rates).

We consider three scenarios for the evolution of age group- and sex-specific prevalence and diabetes-related mortality rates. First, we use the optimistic assumption that age group- and sex-specific mortality and diabetes prevalence stay constant over time (Scenario A). Second, we let the growth of age group- and sex-specific prevalence and mortality rates grow depending on a country's income group classification and adult diabetes prevalence in 2015 as indicated in Table 8 below (Scenario B). The rationale for this approach is that, we assume middle-income countries to increasingly adopt Western sedentary lifestyles and consumption patterns. This trend is likely to be less pronounced in low-income countries where limited budgets constrain rapid changes in consumption patterns. Lastly, in Scenario C, we double all growth rates from Scenario B. As a consequence, our projections cover very optimistic to very pessimistic outlooks.

Table 8

In addition to changes in prevalence and mortality rates, the growth of direct costs depends in part on the remuneration of health personnel, which we assume to account for 60% of overall direct costs per patient. Similarly, the increase of indirect costs depends on the evolution of average annual wages. For all projection scenarios we assume that both averages wages and the remuneration of health personnel grow at the same rate as real GDP per capita.

As depicted in Figure 12 and 13, our estimates suggest that the economic costs for SSA are projected to increase from $19.45 billion (1.2% of GDP) in 2015 to $35.33 billion (1.1% of GDP) in 2030 according to Scenario A, $47.33 billion (1.4% of GDP) in Scenario B and $59.32 billion (1.8% of GDP) in the most pessimistic Scenario C (measured in 2015 prices).

Figure 12

While all projection scenarios place Southern Africa on top with an increase from $12.10 billion in 2015 to $17.15–$29.20 billion in 2030 depending on the scenario, we also predict substantial growth in absolute costs in Eastern Africa, from $3.82 billion in 2015 to up to $16.21 billion in 2030. Relative to GDP, Southern Africa is again predicted to bear the largest economic burden in all projection scenarios (between 3.4% and 5.8% in 2030).

Figure 13

Despite the uncertainties about the future evolution of prevalence and diabetes-related mortality rates as well as future GDP growth, the numbers are alarming. The high direct and indirect economic burden SSA is predicted to face create a strong incentive for policy makers to increase efforts to reduce diabetes-related complications and premature mortality. But, as the analysis of this report shows, health systems in sub-Saharan countries are not prepared to effectively manage diabetes, the current health systems response is weak, the care provided suboptimal and the unmet need very large. The following sections therefore point to potential health policies which

may help SSA countries to better cope with the challenges imposed by diabetes.

If diabetes is effectively managed, its future health and economic burden could be substantially reduced. We explore in the next section potential benefits that could be realised if diabetes in SSA were to be managed according to international guidelines and evidence.

Benefits of scaling up diabetes interventions in SSA

Among people with diabetes, high blood pressure, disordered lipid profiles and poor glycemic control constitute the three principal co-existing risk factors for morbidity and mortality, and an aim of good diabetes care is to prevent their long-term complications. While all three risk factors impact on both large- and small-vessel complications, there are substantial differences in their relative impact, in the complexity of their treatment and monitoring regimens, in their therapeutic window, and in the costs of therapy. There are important interactions between the risk factors for both the large vessel (coronary heart disease, stroke) and small vessel (retinal, renal, neuropathic) complications of diabetes, (217, 218) with treatment guidelines emphasizing the importance of addressing all three (219).

For both blood pressure and lipid therapies, there has been a move towards targeting treatment to individuals at higher levels of risk, rather than according to levels of blood pressure or lipids, with the understanding that different individuals may experience different benefits and risks from therapy depending on their co-morbid conditions. For example, people with previous myocardial infarction or stroke may benefit from being initiated on treatment at lower levels of blood pressure or LDL-cholesterol than others. The risk-based approach to treating blood pressure, termed 'benefit-based tailored treatment' (BTT), has been shown to be more effective and less costly than treating blood pressure to target levels (a 'treat-to-target (TTT) strategy').(220) In addition, when considering BP, lipid, and diabetes control in patients with diabetes, it has been shown that in countries with poor insulin availability (which, as discussed above, reflects the state in many LMICs), BTT was more clinically and cost effective than TTT for preventing micro and macro vascular disease in LMICs. If insulin was available the BTT strategy was no longer superior for preventing microvascular disease. (149)

Using the same model as described in the above manuscript, we tested, a microsimulation model, whether a BTT approach compared to status quo or a TTT approach compared to status quo would overall be beneficial to people with diabetes in countries in SSA for overall diabetes risk factor management. We summarize the methods in panel 9.

Panel 9: benefits of managing diabetes using a BTT or TTT in sSA

We constructed a microsimulation model (methodology published in detail elsewhere (149) and see appendix F) to compare the approaches to reducing the risk of major macrovascular (myocardial infarction, stroke) and microvascular (neuropathy, retinopathy, and end-stage renal disease) complications of diabetes among two populations aged 30-70 years old in SSA, from Malawi (*N*=35,730), participating in the Karonga Prevention Study (221) and from Ghanaian plus South African datasets (N=3,938 and 2,352 respectively), representing the spectrum for SSA.

The methods and limitations have been described in detail elsewhere (149, 220). In summary, two alternative management approaches were compared. The first was a TTT strategy involving titration of blood pressure treatment agents, statins and glucose lowering drugs to predefined targets. The second was a BTT strategy, which comprised treating individuals at high macro-vascular risk with blood pressure treatment agents and statins, and those at high micro-vascular risk with glucose lowering agents, until they achieved low risk levels. Thus TTT strategy involved treating individuals with blood pressure treatment agents until they achieved a blood pressure <130/80 mmHg[256]; with a statin to achieve a low-density lipoprotein level of <2.59 mmol/L (100 mg/dL) (222); and with metformin, sulfonylureas and, if needed, substituting the sulfonylurea with insulin, until they achieve a hemoglobin A1c level of <7% (134, 135). We compared each method with status quo and thence compared average cost effectiveness ratios of BTT and TTT.

The BTT strategy involved treating individuals with a 10-year combined risk of myocardial infarction and stroke >10% with antihypertensive agents and a statin until their risk lowered below the 10% threshold (provided blood pressure remained >110/55 mmHg for safety), and for those with a *lifetime* risk of the three major micro-vascular outcomes (blindness, end-stage renal

disease, and amputation secondary to neuropathic ulcer) of >4%, treating elevated glucose with metformin, sulfonylureas and, if needed, substituting the sulfonylurea with insulin until lifetime micro-vascular risk was below 4% (provided fasting blood glucose remained >3.33 mmol/L [60 mg/dL], for safety).

We employed WHO guidelines for blood pressure medication and statin medication choice, (223)[256] and the Yale Diabetes Center Guidelines for dose escalation algorithms for metformin, sulfonylurea and insulin.(224)

Cases averted, disability-adjusted life-years saved (based on disability weight values estimated by the Global Burden of Disease Project),(225) and drug costs for therapy (based on per-unit global buyer cost estimates from the International Drug Price Indicator Guide) (190) were integrated over the simulated life-course of all persons with diabetes who were alive, or born, during the next 10 years, per standard cost-effectiveness guidelines (226). Additional service delivery costs were assumed to be the same for each strategy.

DALYs and costs were discounted at a 3% annual rate, and costs were expressed in 2016 U.S. Dollars.

We found that from a population perspective a BTT strategy was more effective and more cost-effective than a TTT strategy (Table 9). Although a similar fraction of people with diabetes were typically recommended treatment of any kind (a mean of 86% under TTT versus 88% under BTT in Malawi; see Table 9), those typically treated with the BTT strategy were treated more intensively (4.5 versus 3.5 medications per person, respectively).

As shown in Table 9, the BTT strategy would recommend more adults with diabetes to receive blood pressure lowering agents to a significant extent, and increase to a non-significant extent the number treated with statins and glucose lowering agents, as compared to TTT. Correspondingly, the BTT strategy was estimated to avert two to four times as many macro-vascular events (myocardial infarctions and strokes), but did not significantly differ from the TTT strategy in the number of micro-vascular events prevented.

Using the TTT strategy the estimated total drug costs in 2016 would be $1,346.6 million (CI: 471.1- 2,206.7 million). With the BTT strategy, the total drug costs would be higher at $1,407.9 million (CI: 464.7 - 2,332.5 million).

In terms of total DALYs averted, the benefits of BTT were greater (Table 8), with BTT leading to saving of 1.9 million DALYs (CI: 0.9 – 3.4 million) and TTT 1.2 million DALYs (CI: 1,161.3 (0.6 - 2.1 million).

Table 9

With BTT, the average costs were between $137.5 and $2,600.2 per DALY averted (Mean $743.4) versus $227.6 to $4,047.5 per DALY averted (Mean $1,159.5) for the TTT strategy (Table 9).

The results show substantial benefits of effective scale up of diabetes services to address unmet need. The question remains on the ability of countries to strengthen health systems to respond to the needs.

There are encouraging examples of successful models of diabetes care emerging in low-income countries and in SSA. In the next section we explore these models and provide country case examples of innovative approaches introduced in SSA for effectively managing diabetes to illustrate what might be possible in the future.

Service delivery models for managing diabetes mellitus in SSA

We undertook a review of published studies on current approaches to diabetes care in SSA (appendix G). We also undertook case studies to examine current practices in eight countries (Botswana, Ethiopia, Kenya, Malawi, Mali, Rwanda, Senegal and South Africa) and including detailed studies in Ghana and Tanzania, using a proprietary tool (226), which has been used to analyse tuberculosis(227) , HIV (228, 229)', malaria (230), mental illness (231) programmes in several settings, including several African countries (232), and was adapted for diabetes. In addition, we examined how existing and new technologies could be harnessed to help improve management if diabetes in SSA. We discuss each in turn.

The review identified 467 studies, of which 32 from 11 different countries (Cameroon, Eritrea, Ethiopia, Ghana, Kenya, Malawi, Mozambique, South Africa, Sudan, Tanzania and Uganda) met inclusion criteria. The review revealed that in many SSA countries diabetes care is still largely available only in a hospital setting, requiring patients to travel great distances to access services and follow-up care which is important for effective diabetes management. However, several countries have seen success with the introduction of new, decentralised care delivery models for managing diabetes at PHC, community or home setting, with an emphasis on use of nurses, community health workers (CHW), patient education and community engagement.

Cameroon and Tanzania have introduced community-based management of diabetes.(233) In Cameroon, facility-based interventions for high blood pressure and diabetes with task shifting and nurse-led care in rural health districts significantly improved retention levels for management of patients.(234) Similarly, in Kenya, management of high blood pressure and diabetes has been devolved to rural primary health care clinics with good retention rates and control.(235) In Ethiopia, physicians and diabetes-trained nurses travel from hospitals to peripheral medical centers for training and care provision, with early encouraging results in improving access to services.(236, 237)'

In the public sector in South Africa, a chronic disease outreach programme, which used PHC nurses to provide educational and follow up advice to patients with diabetes, improved early detection and referral of high-risk poorly controlled patients to specialist centres.(238) Decentralisation of diabetes management to community level was also successful in the private sector in South Africa, where the care of diabetes was transferred to PHC physicians working in community-based facilities affiliated with a diabetes and endocrinology centre. The scheme used community-based capitation and risk-sharing model for diabetes management and led to major reductions in hospital admission rates for both acute metabolic emergencies and all causes, reduced costs, delayed progression of micro-vascular complications, and improved outcomes.(239) Nurse-led diabetes care, with nurse-led protocol and education-based system, was also shown to be successful in rural Kwazulu Natal in South Africa with improved control of HbA1c levels, and higher satisfaction for patients, their families and health workers.(240) Although, the improvements in glycaemic control achieved at 18 months following the

introduction of the scheme were not sustained at 48 months, the HbA1c levels at 48 months were lower than baseline figures. (241) As with South Africa, the introduction of protocol-driven nurse-led management of diabetes in PHC setting in rural and urban Cameroon also led to improvements in glycaemic control and blood pressure. (242) However, a study of CHW model of outpatient care introduced in South Africa for diabetes and hypertension, which involved monthly home visits, counseling services and access to monthly supplies of medication, showed improved hypertension control but not diabetes, with 26% of the patients at the clinic showing improved diabetic care compared with 9% of the CHW-targeted home visit patients. (243)

In combination with decentralisation of services, plans to specifically integrate care have been successful. In Cameroon, integration of care for high blood pressure and type 2 diabetes was effectively achieved in eight rural health districts by task shifting to non-physician clinician facilities, with improved control in patients attending services. (243)

In South Africa home glucose monitoring using urine testing was introduced 30 years ago, even for illiterate patients, with good compliance and lower random glucose levels compared to non-compliers. (244) In Kenya, a home glucose-monitoring programme that used mobile phones to enable CHWs to regularly communicate to patients to modify the dose of insulin injections helped to improve HbA1c levels. (245, 246)

Patient education has also been used in several settings to improve services across the care continuum and to decentralise care away from hospitals to patient level. For example, in Cameroon, motivational counseling and education was integrated into a screening program to improve rates of follow-up for newly diagnosed individuals.(247) In South Africa group education was used at community health centers to improve patient's knowledge and management of diabetes, but there was no improvement in diabetes self-care activities, weight loss, HbA1c levels and quality of life, or improvements in self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, and mean total cholesterol levels.(141) Another study from South Africa showed that group education programme for patients with Type 2 Diabetes could be implemented in rural areas with a dietician or health promoter to provide a supportive environment for patients for learning and coping with significant improvement in adherence to a diabetic diet, physical activity, foot care and the perceived ability to teach others, but no

significant change in smoking or adherence to medication.(248) In Tanzania, a hospital-based education programme for children with Type 1 Diabetes on symptom management, correct insulin storage and insulin administration led to reductions in severe hypoglycaemia, but no improvement in HbA1c levels.(249) In Mozambique, twinning programmes have been used to successfully establish patient education programmes and to improve their effectiveness. (183)

In addition to patient education, health-provider education at hospital, PHC and community levels has been used to improve early recognition of diabetes and diabetic sequelae, and to enhance disease management in SSA. In Tanzania, where 70% of leg amputations occur in diabetic patients, training of healthcare personnel at different levels in diabetic foot management has led to improved case finding, earlier referrals, establishment of well-functioning foot clinics, and strengthened management of diabetic foot ulcers with better health outcomes.(103) In Eritrea, a co-operative diabetes project, which emphasised multidisciplinary training of physicians, laboratory scientists, diabetes nurse practitioners, patient educators, and dieticians and improved quality of laboratory services, led to improved management of diabetes with better HbA1c levels.(250) Multidisciplinary training for diabetes, involving physicians, dietitians and nurse educators and pharmacists has also been introduced in Ghana to strengthen diabetes services (251), while training of patient educators has been introduced in Sudan (252).

In SSA, electronic medical records (253), treatment protocols, and guidelines(254) have facilitated the development of primary care, community and home-based service models. For example, Malawi has successfully used existing service delivery platforms and expertise for tuberculosis management that has well-established treatment guidelines as well as monitoring and reporting mechanisms.(255)

Integrating diabetes and hypertension care into existing chronic care models for HIV has also been mooted as a promising strategy. South Africa has used mobile units for HIV counselling and testing as an entry point for combined screening of high blood pressure and diabetes, with high yield of new cases, but linkage to care and follow up was challenging.(256) Community-based HIV testing campaigns were used in Uganda to simultaneously offer diagnostic, preventive, treatment and referral services for HIV, malaria, tuberculosis, high blood pressure and diabetes, with effective linkage to care.(257) In Kenya, HIV counsellors were trained to screen for diabetes and

high blood pressure in home-based screening, and district hospital based staff to conduct community-based screening, with effective uptake for both approaches, but in both follow-up levels were low, with one fifth of patients returning after a random glucose test.(246)

African experience of diabetes management suggests a particular distinctiveness with strong reliance on non-physician health workforce including nurses, community health workers, and health extension workers, as well as traditional healers in some settings. Several countries, such as Botswana, Ghana, Ethiopia, Kenya, Malawi, Mali, Rwanda, Tanzania and South Africa included in the study, have introduced innovative approaches to address resource constraints when managing diabetes (See Panel 10 for a summary of initiatives for and barriers to providing diabetes care in selected countries where Commissioners work. These in country case studies are published in full as Comments [references x-z]).

Panel 10: Country experiences in managing diabetes in SSA (for references see Comments)

In Botswana patients with diabetes have access to general nursing, psychology, and social work services both in the private and public sector – where CHW and diabetes youth leaders provide education and public health screening campaigns. In Ghana, facilities for diabetes treatment are available in urban areas, but despite the planned expansion of services in the 2014 NCD Strategic Plan the majority of the urban population and the rural populations remain without access to diabetes care.

In Ethiopia, diabetes services are delivered mainly at PHC centres. Specialised clinics located in the major university teaching hospitals also provide diabetes care by endocrinologists or general internists. Nurses, health officers and general practitioners provide most of the diabetes care in health centres and general hospitals. In 2014, an estimated six out of 10 health facilities, excluding health posts provided diabetes care, but the majority of patients with diabetes are undiagnosed.

Following the launch of the national diabetes strategy in 2010 Kenya began to expand diabetes services, with training of healthcare professionals and CHW, national guidelines, and diabetes screening, but services at community and PHC levels are hampered by inconsistent availability of

drugs and diagnostic equipment.

Malawi has low numbers of health workforce and resource shortages, and patients with diabetes are under diagnosed and poorly controlled. However, it is piloting the WHO package of essential NCD interventions for PHC care in low-resource settings and has set a target to train 1000 health workers by 2016. It has introduced new service delivery models for diabetes that mimic DOTS approach used in tuberculosis care, and home-based care and peer-support used in management of HIV.

Rwanda is introducing clinical NCD services and care package across all health facilities, and a 'NCD clinic model' in district hospitals and health centers. As a result, the number of people living with diabetes and requiring close follow-up has increased.′ To address shortage of health professionals and increasing demand, Rwanda has introduced pre-service and in-service training for existing staff for management of NCDs, started a programme of task shifting to transition chronic disease management to home setting, and created a new cadre of health professionals – Home Based Care Practitioners – at community level to provide home-based services for diabetes and other NCDs.

In 2011, Tanzania established a National Diabetes Program as collaboration between the Ministry of Health and Social Welfare and the Tanzania Diabetes Association – the implementing agency for the Program – which has used existing government facilities and staff to establish 148 diabetes clinics in zonal, regional and district hospitals. Using funding from international agencies and the private sector it provides funding for equipment and training of personnel to provide care for around 800,000 people with diabetes. Diabetes care is provided free of charge to patients and government mandates that diabetes drugs should be given for free to patients using district and regional diabetes clinics.

In South Africa, diabetes care is provided in the public and private sectors, but huge inequities exist: the public sector caters for 84% of the population and spends $140 per person per year (4.2% of GDP), while the private sector for 16.4%, spending $1,400 per person per year (4.3% of GDP). A network of National Health laboratories provides services to over 80% of the population for all standard diabetes related investigations, but not all PHC clinics have access to standard

diagnostic equipment due to budgetary constraints.

Harnessing new technologies to improve diabetes care in SSA

New technologies currently available for diabetes care were developed for use in resource-rich health systems, but not for SSA where: (i) necessary technologies do not exist – requiring the development of low-cost health technologies (ii) technology exists but is not accessible – due to high cost, and (iii) accessible technology is not adopted – as a result of health system barriers.

(i) Developing low cost, affordable technologies for SSA

Most of the health technologies used to diagnose, monitor and treat diabetes and its complications are not affordable to patients in SSA. Patients experience difficulties in accessing health centres and when they do incur impoverishing expenditures. (172, 173, 258-261)

Low-cost and accurate diagnostics for point-of-care testing of blood glucose, HbA1c, glycosuria and proteinuria could improve screening, diagnosis, treatment initiation, and monitoring of diabetes and help mitigate access constraints in delivering effective diabetes care, particularly with distributive model of PHC- and community-based services provided by community health workers (Panel 10).

Panel 10: Affordable cost-effective technologies for diabetes care in SSA Effective early detection of diabetic retinopathy, which may reduce the risk of blindness by 95%, currently requires both clinical staff with ophthalmological training and costly equipment to carry out eye exams. Both requirements are a major obstacle to care, as illustrated by the case of Malawi, which has 16.4 million inhabitants but just six ophthalmologists. New devices such as the "The Portable Eye Examination Kit (PEEK)" app (http://www.peekvision.org) which uses a smartphone and the hand-held "epiCam" device (http://www.epipole.com/epicam/) which can capture images digitally for store-and forward using a lap-top computer, offer the possibility of screening for diabetic retinopathy by health workers in PHC, community-based services and in remote rural areas. While these devices rely on expert analysis for interpretation of fundus images, diagnostic algorithms could be used to remotely analyse and grade images at considerably low cost. However, supporting reliable infrastructure needs to be in place to allow the widescale adoption of such technology. Automated

grading of fundus photographs is used within established services including the Scottish National Diabetic Retinopathy Screening Programme and has been studied in Nakuru, Kenya.(262)

Peripheral neuropathy is another important complication of diabetes where there is an urgent need for new diagnostics tools for early detection. The prognosis for diabetic peripheral neuropathy is poor if not diagnosed early. But, accurate diagnosis of diabetic neuropathy represents a major challenge, even in the context of resource-rich health systems. (263) The development and adoption of new non-invasive diagnostic devices that enable point-of-care testing and not require specialised training to use, for example SUDOSCAN (http://www.sudoscan.com) and NC-stat DPNCheck (http://www.dpncheck.com), could improve screening and early detection of diabetic peripheral neuropathy in resource poor settings.

Low cost diagnostic devices that enable point-of-care testing of blood glucose, HbA1c, glycosuria and proteinuria could be used for screening, diagnosis, treatment initiation, and monitoring. However, although relatively low cost, affordable devices do exist, numerous manufacturers produce such devices, and there is often little compatibility between the equipment (for example, blood glucose sticks) needed for such devices and even for some manufacturers own models. Pushing diagnostics device manufacturers to make changes towards greater interoperability, however, will necessitate a more centralised approach towards procurement of diagnostics devices used in the management of NCDs. Moreover, international bodies such as WHO have an important role to play in developing the technical standards required for better integrated diagnostics infrastructures for NCDs such as diabetes, just like these bodies did in strengthening diagnostics service infrastructures for infectious disease such as HIV and TB.

There is, hence, a need for better interoperability of technologies developed by companies to ensure that low cost models can be used in LMICs with interchangeable disposable components. Once this hurdle is overcome, the results from such devices, can be used in combination with mobile or smart phones to target messaging for prevention (264), communicating test results (265) , self-monitoring of diabetes (266) (to help improve

adherence), or to attend clinics when needed . Affordable diagnostics and communication technologies could help transform diabetes care, as they have done for HIV management in resource-poor settings (267, 268).

Cloud-based systems offer the possibility of capturing data from multiple sources and devices in real-time and their integration. Data cloud solutions are low cost and more scalable than traditional data storage systems (reliant on hardware requiring constant electricity supply and regular servicing). By integrating data from multiple devices and sources, cloud-solutions can help manage the complex data needed across multiple facilities, levels and over long periods of time for management of diabetes and help develop better understanding of the epidemiology of diabetes and responses to interventions.

(ii) Improving access to existing technologies for better diabetes care in SSA

Ensuring timely and affordable access to existing cost-effective technologies, such as appropriate forms of insulin (269) , medicines, miniaturised blood glucose sensors, and strips for testing of urinary glucose of protein, is a challenge in SSA. Improved technology assessment, procurement and supply chain management can help to achieve greater value for money, and timely delivery of available medicines to avoid treatment interruptions and expand access.(270)

Strategies for better use of cost-effective technology should emphasise both 'health technologies' (such as new therapeutics, diagnostics, and medical devices) and 'technologies for health' (technologies such as communication and transport which impact on health). These strategies should foster investments in 'hard' (infrastructure and equipment) and 'soft' technologies (information and communication technology [ICT] with data analytics for example).

In SSA ICT has been used variously in HIV and tuberculosis programmes (271), but overall, its use in health systems is low. Diabetes registries – that form the mainstay of diabetes care platforms in HICs – are only available in 17% of countries in the entire WHO Africa region (81). One possibility is to extend databases for HIV and tuberculosis where they exist for diabetes and NCDs. Where no such systems exist, development of future-proof diabetes registries is a priority.

The absence of legacy systems provides an opportunity to introduce cost-effective ICT solutions that use mobile telephony (272-274) to facilitate data sharing. For example, existing solutions using 'cloud technologies' offer an important opportunity to capture and integrate real-time data across multiple mobile phones, point of care devices, laboratory diagnostics, and electronic health records (panel 10).

(iii) Improving the adoption and diffusion of new health technologies for diabetes care in SSA

The third challenge that needs to be addressed in relation to technology relates to factors that hinder adoption and diffusion of new technologies. These factors include imprecise definition of the problem being addressed, complexity and scalability of the technology or intervention, resistance from the adoption system (health professionals and service users for example), characteristics of the health system that create rigidities or provide inadequate incentives, and poor recognition of the challenge of diabetes in the broader context (among the population and the politicians) such that it is not considered as an urgent and major societal challenge.(275, 276)'

In SSA, emerging care delivery models for diabetes have distinctive features: a public health approach, with simplification and decentralisation of care to PHC and community levels, with strong reliance on non-physician health workforce (including nurses, community health workers and health extension workers), community involvement, peer support and, self-management. Expanded access to existing technologies can help SSA to not replicate Western models of care - which often favours an expert led approach – but to foster innovative delivery models that reflect the African context, and build on experience of the innovations in care delivery with HIV/AIDS (277, 278)'. Indeed if this is successfully implemented, Western models of diabetes care could learn a lot from SSA.

Creating a successful response to diabetes in *in SSA*

Health systems in SSA are unprepared for the rapidly rising burden of diabetes. Consequently, many people go undiagnosed, and those that are diagnosed are not screened for comorbidities, do not receive treatment, or are not adequately controlled. The resultant morbidity and mortality leads to immense human, economic, and societal loss.

Diabetes, a long-term condition associated with multiple vascular risk factors and sequelae, and its increasing prevalence in SSA reflects not just a disease, but also a changing phenotype. The approach to managing such a complex and heterogeneous disorder has to be multi-sectoral, with literacy, engagement and co-operation of the person involved, with awareness and education within the community. Specific therapeutic measures are not enough; successful management of diabetes in SSA requires an enabling medical, social and political context within which effective prevention, screening, diagnosis, treatment and lifelong care can be delivered. In this respect, there are lessons to be learned from the HIV response in Africa, which successfully brought together governments, civil society, healthcare providers, community, donors and private sector.

The sheer burden of diabetes in SSA and its impact on individuals, populations, health systems and economies, means that policy-makers must act to bring together wide ranging stakeholders to spur action at country and global level around a set of ambitious yet achievable targets, linked to those set in the Sustainable Development Goal (SDG) 3, 'Ensure healthy lives and promote well-being for all at all ages'. Of the 13 targets set for SDG 3, six are most readily applicable to diabetes in SSA. These include:

(i) By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment

(ii) Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all

(iii) Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate

(iv) Support the research and development of vaccines and medicines for the communicable and noncommunicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines

(v) Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries

(vi) Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks (not just for infectious

diseases, but also for diabetes and other NCDs)

In addition, countries in SSA should embrace the nine voluntary targets (to reduce premature mortality due to NCDs by 25%, reduce physical inactivity by 10%, reduce tobacco consumption by 30%, achieve a 25% reduction in high blood pressure, achieve 80% coverage of essential medicines and technologies for NCDs and achieve 0% increase in the prevalence of obesity and diabetes by the year 2025) adopted at the 65th World Health Assembly by member states as part of the WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020.(185) A Global Monitoring Framework underpins the Global Action Plan, with 25 indicators that are monitored by member states – of which 12 are relevant to diabetes, and can be used to monitor achievements in SSA. (279)

Achieving the targets set in the SDG 3, and the Global Action Plan would undoubtedly help transform the fight against diabetes in SSA, help avert needless suffering and death, and reduce the economic burden of diabetes on individuals, households and societies. The critical ingredients of an effective response are solidarity and collective action at local, national, African and Global level – with clear responsibilities for stakeholders as part of a collective response. The elements of this collective response, on which the Commissioners agree are a priority, are laid out below. We also have also detailed operational targets which are achievable by 2020, 2025, and 2030 in Panel 1.

Governments

Ultimately, governments should respond to the needs of their populations. In addition to enabling access to health services, governments should seriously consider introducing public health measures to impact NCDs by banning smoking in public places, restricting advertising, increasing taxes on cigarettes and sugar sweetened beverages, and limiting portion size of sugar sweetened beverages (33, 280).

A health-literate population is critical for generating demand, improving access to the health system and ensuring uptake of preventative measures. Much of the increase in health literacy in SSA has come from successful media campaigns via radio, poster adverts, and education via interaction with CHWs. These campaigns have generally focussed on prevention of HIV (e.g.

condom use) and malaria (e.g. use of insecticide treated bed nets). Investment and research is now needed to build on these initiatives and increase population's awareness of diabetes and to generate demand. Therefore, we recommend that countries in SSA research and develop locally appropriate media campaigns to educate the public about the symptoms of type 1 and type 2 diabetes, and encourage those with symptoms to seek care. In particular, media campaigns should be deployed to educate citizens about preventative lifestyle measures, combined with government regulations that limit advertisements for unhealthy foods.

We recommend that governments should allocate sustainable funding to tackle the diabetes epidemic. We have estimated that in 2015 the economic burden of diabetes in SSA was $19.45 billion, or 1.2% of cumulative GDP of the whole of SSA. Unchecked, this economic burden is projected to increase to between $35.33 billion and $59.32 billion by 2030, equal to 3.4%–5.8% of GDP in Southern Africa, 1.1%–1.7% in Eastern Africa, 0.9%–1.5% in Middle Africa and 0.3%–0.5 in Western Africa.

Given the strong causal link between NCDs (including type 2 diabetes), sugar sweetened beverages, salt, and tobacco, we strongly advise countries to consider raising revenues by taxing these products to fund health systems. Although, all-too-often, considered as a disease of the rich, in SSA the burden of type 2 diabetes is increasingly borne by the poor (21). Making available and encouraging healthy choices and taxing unhealthy choices should help promote health of the poorer sectors of society, whilst raising revenue for treasuries to finance health systems and expand access to effective health care.

Such taxes should be combined with national health system assessment and actions to establish effective and efficient responses to burden of diabetes to further expand fiscal space. Assessments should detail the burden of diabetes and its co-morbidities, their management at all levels of the health system, a detailed exploration of the capability of human resources, availability of drugs and equipment and their costs (to individuals and health system) and functioning of supply chain management, and how the services and platforms developed for communicable diseases can best be leveraged to also provide services for diabetes. In line with this, governments should prioritise data collection for the improvement of their population health. There is an urgent need for integrated digital health information systems to capture data

on diabetes, its comorbidities, and their management in health systems, with timely analysis to inform planning and improved care.

Diabetes and its sequelae can be treated cost-effectively most of the medicines required are on the WHO 2015 essential medicines list, off-patent and affordable. In addition, ACE inhibitors for protection against microvascular disease, should be made available (for example enalapril, which is currently listed as an antihypertensive on WHO list of essential medicines) and diabetic retinopathy. (281) Insulin is a special case, as generic forms are not widely available. However, countries can purchase vials of human insulin at prices comparable cost per person per year to that paid for one-year supply of fixed-combination ARV treatment. Given the absolute need for insulin treatment for type 1 diabetes and increasing need for type 2 diabetes, human insulin should be widely available for all those who need it. We consider that in the context of low-income countries of SSA, more expensive analogue insulins do not provide enough extra benefit to justify their current costs. (146) Considering treatment, we urge countries to make all necessary medicines on the WHO essential medicine list for diabetes, hypertension, and cardiovascular disease available at no cost to all patients who need them. While newer treatments for type 2 diabetes may have some benefit over standard oral anti-hyperglycaemic agents and insulin, these could be considered a worthwhile investment for the public sector once the countries have been able to provide essential services and medicines for diabetes.

Human resource shortage is a critical challenge, and there is an urgent need to educate and train all groups of health professionals – ranging from community health workers to specialist physicians at all levels of the health system – on the management of diabetes along the care continuum to enable increased detection improved treatment. Training need is especially great in settings dealing with children, so that a diagnosis of type 1 diabetes is not fatally missed, in areas of maternal health to ensure diagnosis and treatment of gestational diabetes, and to effectively manage interactions between diabetes and communicable diseases. Once recognised, diabetes – especially type 2 – can be effectively managed. Hence, we would advise countries to consider leveraging existing human resources by training them to diagnose and treat diabetes, and by using cost-effective technologies, before investing in training of specialist diabetologists.

The sequelae of diabetes are insidious and present late in the disease course. Their effective

management requires yearly monitoring at well-equipped health centres with health care professionals able to manage glycaemia and other cardiovascular risk factors, and screen for complications, in order to improve macro and micro-vascular outcomes. It is essential to ensure that adequate referral pathways are in place to ensure regular monitoring and management of complications.

To minimise OOP indirect costs from attending multiple separate clinics, services for diabetes, other cardiovascular risk factors, and chronic complications should be integrated, wherever possible.

Overall governments should work towards Target 3.8 included in the SDGs: "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all"

Civil Society

Civil society plays a critical role in catalysing change to improve access to health care and in holding governments to account. Advocacy from civil society was instrumental in the global movement for HIV, which prompted the convening of a special session of the UN General Assembly in 2001 and led to the first UN declaration focusing on a disease. (282)
Civil society could frame diabetes as an integral part of the global commitments to address NCDs and to achieve UHC, given its links to so many risk factors and conditions, and use this narrative for awareness building and mobilising support among a broad range of stakeholders.

Effective deployment of civil society requires strengthening and expanding networks, and improved modes of communication. In many of the countries in SSA, diabetes organisations are playing a key role in educating the public, health care providers, and governments about diabetes (see in country case studies – appendices x-z). We recommend that across SSA diabetes organisations should continue to catalyse the continuing improvement in management of diabetes by tracking progress towards objectives set out in national NCD or diabetes plans and holding governments to account for their implementation. However, funding is needed to ensure sustained engagement of civil society. We urge donors and diabetes organisations in other countries to consider funding and, or partnering with foundations in SSA to enable mutual

learning, strengthen the agenda for change and to ensure sustainability. The involvement of global NCD advocacy organisations, for example, the IDF, NCD Alliance and World Heart Federation, have a key role in supporting local organisations in SSA.

Of particular urgency is type 1 diabetes, where it is suspected, although not definitively known, due to lack of data, that the majority of sufferers may die without a diagnosis or access to treatment. Civil society should play a key role in raising awareness of type 1 diabetes and t ensure that governments are held accountable regarding guaranteeing a supply of insulin to all sufferers, not just children

To date, most international health NGOs have focused on maternal, neonatal, and child health, communicable diseases, and on providing health care in conflict settings. While some NGOs, such as IDF Life for a Child (http://www.idf.org/lifeforachild) and Sante Diabete (http://www.santediabete.org/en/), have focussed on diabetes, these are exceptions. It is encouraging to note that Médecins Sans Frontières (MSF) (http://www.msf.org) is increasing its involvement in NCDs (283).

We encourage NGOs working in SSA to recognise the importance of diabetes and obesity in the populations they care for and, where possible, work in concert with country health systems to find solutions to improve diabetes care. This is particularly important for NGOs who deal with communicable diseases and improving maternal and neonatal health, where diabetes impact on outcomes.

International Donors

While NCDs have been identified as a priority at the 2011 UN High Level Commission (284), with renewed commitment in SDG 3, they still do not feature prominently on the agendas of most global health funders (10) whose financial assistance to countries has plateaued. To date, few donor agencies have provided assistance for NCDs or diabetes.

We do not know whether this lack in attention is due to overweight, obesity, and diabetes being perceived as 'lifestyle' problems, or because they are unlikely to pose the perceived threat to health in high income countries that infectious disease do, or perhaps entirely different reasons

make them less easy for international donors to 'market' to their supporters as worthy areas for investment. Yet, evidence strongly suggests that overweight, obesity, and diabetes are influenced more by environment than individual factors. In addition, there is an imperative to invest in management of NCDs if the health gains due to improvements in maternal, neonatal, and child health, communicable diseases are to be sustained. Hence, donors should increasingly invest in health systems to benefit NCDs, communicable diseases, and maternal and child health.

Global agencies

As with international donors, global agencies have been slow to transition to a new world where NCDs predominate. The 2011 United Nations High Level Meeting on NCDs (11, 284) produced the UN General Assembly Resolution (285), committing UN member states to the prevention and control of NCDs. In 2013, at the 65th World Health Assembly member states agreed to reduce premature mortality from NCDs by 25% by the year 2025 relative to their 2010 levels. (286) However, in relation to action apathy prevails.(287) Although a global coordination mechanism, a monitoring framework, an action plan, and an UN interagency task force have been established, their benefit to those living with NCDs in country is not clear enough, given that targets were supposed to be met in 2025 (in only 8 years).

WHO need to be engaged in the production of straightforward guidelines and lists for countries to look to for improving NCD care. For example, lists of essential diagnostics for NCDs (akin to the essential medicines list) could be very valuable.

WHO is well respected in SSA and is well placed to play a leadership role. It also has the legitimacy to work with member states, international agencies and civil society organisations to mount an urgent and coordinated response to diabetes. However, this opportunity can only be realised if WHO acts on the criticisms (288) and lessons from the Ebola crisis to emerge as a leader in the battle against diabetes and NCDs. In addition to leading the response in countries, an under-resourced WHO should follow a collegial route, more widely involving external collaborators in efforts to support the diabetes response. (24)

The World Bank with its development capability, the Global Fund, with its financing prowess, UNITAID, with expertise in innovative financing and creation of market dynamics to expand

access to health technologies and medicines, GAVI, in effective partnerships to expand access to vaccines, USAID, in reproductive, maternal and child health, and UNICEF in building effective platforms established for managing children's problems could catalyse an integrated response to NCDs.

Research, development and innovation

A global response to diabetes would not be possible without an effective research and development (R&D), and an innovation agenda to strengthen health systems, develop affordable technologies and medicines, and find innovative financing and service delivery solutions (276, 289)'. Throughout this report we have highlighted, in numerous places, the lack of evidence from SSA that is necessary to inform an appropriate broad-based health system response to deal with diabetes, its complications, and other cardiovascular risk factors. This lack of knowledge is seen at all levels – from determining which measures to use to define diabetes, to defining burden burden of disease, to making treatment decisions, and to planning health system development. Whilst there are some studies in the region, these are often small, out of date, or of poor quality. Our concern is that many of these have been assimilated into larger papers and reports, and will become instrumental in defining a response to diabetes in the area which may be wholly inappropriate to needs. There is a critical need for high quality studies done in SSA that are geared towards ensuring an effective health system response. To date, research funding to deal with diabetes and other NCDs in LMICs, including those on SSA has been woefully inadequate. However, given the urgency of the situation, we cannot advocate a purist approach of implementation only after the results of well conducted research studies have reported. We do, however, strongly urge that all strategies that are implemented in the region using implementation science methodology and done on the background of a firm knowledge of baseline needs (including an accurate, population level, assessment of burden) and that outcomes assessment is integrated firmly into any strategy. We also firmly believe that no program of healthcare will truly maximize its potential unless there is local ownership – this necessitates co-development of research and implementation programs with local users and providers.

The shortage of health professionals is a major barrier to expanding services in SSA, but given resource constraints the near term rapid expansion in numbers is not realistic. Hence, addressing human resource shortages will require a combination of strategies. The first of these strategies is task shifting or task sharing, which has been effectively implemented in SSA to engage a broader

group of health professionals in diabetes care. The second is to leverage novel technologies advances in communications, including distance learning and e-learning through use of online courses to improve the knowledge and competences of existing health workforce.(290) The third, among others, is to use mobile technologies and SMS text messaging to better manage communications and processes in health systems, for example in communicating results (265), attending clinic appointments (267), scaling up public health and prevention interventions (264), and to improve self-management of long-term illness (291).

There are also opportunities for increasing financing diabetes. In spite of the global economic crisis, countries in SSA have achieved sustained economic growth, which is projected to continue in the next decade. (292) In addition, innovative financing (such as Airline Solidarity Levy and Debt2Health), which has been used successfully for AIDS, tuberculosis, malaria and children's immunisation programmes, offers possibilities for funding health systems and diabetes care (293, 294), as well as late stage research (295).

Conclusion

With rapid socioeconomic transitions occurring in SSA, there is a risk that rising prevalence of diabetes (and associated noncommunicable diseases) will overwhelm already struggling health services, and have adverse consequences for individuals and economies. The Commission therefore chose to focus on this region as a priority, although our findings could be translated to other countries facing similar challenges.

Our methods consisted of extensive reviews of the literature, soliciting expert opinion, conducting primary research studies, and convening Commissioners' meetings to discuss findings, challenges, and solutions. The major limitation that runs throughout all elements of the Commission is a lack of reliable data to inform findings. The findings presented within the document are, however, robust to the current state of knowledge in the region and this resultant document should therefore provide pivotal reading for all members of the health care community (from health care worker, to ministers of health, to heads of global development agencies) who aim to improve care for people with diabetes in SSA. The finding of a lack of reliable data is also a Key Message of the Commission and more needs to be done to address the

data dearth in the region.

We conclude that SSA is not prepared for the rising burden of diabetes brought by rapid transitions. Effective management of diabetes in SSA will require careful considerations on expansion of services to meet current and future burden, whilst ensuring that services are integrated with service for other chronic diseases. The health, economic and societal consequences of inaction are huge. Decisive action is needed now by all stakeholders to address the scale and urgency of diabetes in SSA.

1. Geldsetzer P, Barnighausen T. Late-stage research for diabetes and related NCDs receives little funding: evidence from the NIH RePORTER tool. Lancet Diabetes Endocrinol. 2016.
2. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet.388(10053):1459-544.
3. Bank W. World Bank. Health Nutrition and Population Statistics 2016 [Available from: http://data.worldbank.org.
4. Kengne AP, June-Rose Mchiza Z, Amoah AGB, Mbanya J-C. Cardiovascular Diseases and Diabetes as Economic and Developmental Challenges in Africa. Progress in Cardiovascular Diseases. 2013;56(3):302-13.
5. Evaluation IfHMa. The Global Burden of Disease [Available from: http://www.healthdata.org/gbd.
6. Levitt NS. Diabetes in Africa: epidemiology, management and healthcare challenges. Heart. 2008;94(11):1376-82.
7. Manne-Goehler J, Atun R, Stokes A, Goehler A, Houinato D, Houehanou C, et al. Diabetes diagnosis and care in sub-Saharan Africa: pooled analysis of individual data from 12 countries. The Lancet Diabetes & Endocrinology. 2016;4(11):903-12.
8. World Development Indicators 2016: World Bank; 2016 2016/04/27.
9. Allen L. Non-communicable disease funding. The Lancet Diabetes & Endocrinology.5(2):92.
10. Dieleman JL, Schneider MT, Haakenstad A, Singh L, Sadat N, Birger M, et al. Development assistance for health: past trends, associations, and the future of international financial flows for health. Lancet. 2016;387(10037):2536-44.
11. Nations U. High-level Meeting on Non-communicable Diseases [Available from: http://www.un.org/en/ga/president/65/issues/ncdiseases.shtml.
12. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. The Lancet. 2016;387(10027):1513-30.
13. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. The Lancet.387(10027):1513-30.
14. WHO. Global report on diabetes Geneva: World Health Organisation; 2016 [Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf.
15. Federation ID. IDF Atlas, 7th edition. Report. Belgium, Brussels 2015.
16. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, et al. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. The Lancet Diabetes & Endocrinology. 2014;2(4):279-88.
17. Warren B, Pankow JS, Matsushita K, Punjabi NM, Daya NR, Grams M, et al. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. The Lancet Diabetes & Endocrinology.5(1):34-42.

18. Riley L, Guthold R, Cowan M, Savin S, Bhatti L, Armstrong T, et al. The World Health Organization STEPwise Approach to Noncommunicable Disease Risk-Factor Surveillance: Methods, Challenges, and Opportunities. American Journal of Public Health. 2016;106(1):74-8.
19. Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331 288 participants. The Lancet Diabetes & Endocrinology. 2015;3(8):624-37.
20. Werfalli M, Engel ME, Musekiwa A, Kengne AP, Levitt NS. The prevalence of type 2 diabetes among older people in Africa: a systematic review. The Lancet Diabetes & Endocrinology. 2016;4(1):72-84.
21. Tian Y, Jiang C, Wang M, Cai R, Zhang Y, He Z, et al. BMI, leisure-time physical activity, and physical fitness in adults in China: results from a series of national surveys, 2000–14. The Lancet Diabetes & Endocrinology. 2016;4(6):487-97.
22. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat Rev Endocrinol. 2016;12(10):616-22.
23. Bennett PH, Magliano DJ, Alberti KG, Zimmet P. Liberating non-communicable disease data. Lancet Diabetes Endocrinol. 2016;4(10):815-6.
24. Davies J, Yudkin JS, Atun R. Liberating data: the crucial weapon in the fight against NCDs. The Lancet Diabetes & Endocrinology. 2016;4(3):197-8.
25. Hall V, Thomsen RW, Henriksen O, Lohse N. Diabetes in Sub Saharan Africa 1999-2011: Epidemiology and public health implications. a systematic review. BMC Public Health. 2011;11(1).
26. Scott A, Ejikeme CS, Clottey EN, Thomas JG. Obesity in sub-Saharan Africa: development of an ecological theoretical framework. Health Promot Int. 2013;28(1):4-16.
27. Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. The Lancet. 2010;375(9733):2254-66.
28. Kengne AP, Echouffo-Tcheugui J-B, Sobngwi E, Mbanya J-C. New insights on diabetes mellitus and obesity in Africa–Part 1: prevalence, pathogenesis and comorbidities. Heart. 2013;99(14):979-83.
29. O'Hara EG, Nuche-Berenguer B, Kirui NK, Cheng SY, Chege PM, Buckwalter V, et al. Diabetes in rural Africa: what can Kenya show us? The Lancet Diabetes & Endocrinology. 2016;4(10):807-9.
30. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. The Lancet. 2016;387(10026):1377-96.
31. Monteiro CA, MH DAB, Conde WL, Popkin BM. Shifting obesity trends in Brazil. Eur J Clin Nutr. 2000;54(4):342-6.
32. Ziraba AK, Fotso JC, Ochako R. Overweight and obesity in urban Africa: A problem of the rich or the poor? BMC Public Health. 2009;9(1).
33. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev. 2012;70(1):3-21.
34. Development IFfA. Rural Development Report, Chapter 3: Structural and rural transformation in Africa. 2016.
35. Pampel FC, Denney JT, Krueger PM. Obesity, SES, and economic development: a test of the reversal hypothesis. Soc Sci Med. 2012;74(7):1073-81.
36. Aitsi-Selmi A, Bell R, Shipley MJ, Marmot MG. Education modifies the association of wealth with obesity in women in middle-income but not low-income countries: an interaction study using seven national datasets, 2005-2010. PLoS One. 2014;9(3):e90403.
37. Murphy GA, Asiki G, Ekoru K, Nsubuga RN, Nakiyingi-Miiro J, Young EH, et al. Sociodemographic distribution of non-communicable disease risk factors in rural Uganda: a cross-sectional study. Int J Epidemiol. 2013;42(6):1740-53.

38. Gillman MW. Prenatal famine and developmental origins of type 2 diabetes. The Lancet Diabetes & Endocrinology. 2015;3(10):751-2.
39. Lelijveld N, Seal A, Wells JC, Kirkby J, Opondo C, Chimwezi E, et al. Chronic disease outcomes after severe acute malnutrition in Malawian children (ChroSAM): a cohort study. The Lancet Global health. 2016;4(9):e654-62.
40. Gill GV, Mbanya JC, Ramaiya KL, Tesfaye S. A sub-Saharan African perspective of diabetes. Diabetologia. 2008;52(1):8-16.
41. United Nations, Department of Economic and Social Affairs, Population Division, World Fertility Report 2013: Fertility at the Extremes. Population and Development Review. 2015;41(3):555-.
42. Feero WG, Guttmacher AE, McCarthy MI. Genomics, Type 2 Diabetes, and Obesity. New England Journal of Medicine. 2010;363(24):2339-50.
43. Helgason A, Palsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnarsdottir S, et al. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. Nat Genet. 2007;39(2):218-25.
44. Adeyemo AA, Tekola-Ayele F, Doumatey AP, Bentley AR, Chen G, Huang H, et al. Evaluation of Genome Wide Association Study Associated Type 2 Diabetes Susceptibility Loci in Sub Saharan Africans. Front Genet. 2015;6:335.
45. Yako YY, Guewo-Fokeng M, Balti EV, Bouatia-Naji N, Matsha TE, Sobngwi E, et al. Genetic risk of type 2 diabetes in populations of the African continent: A systematic review and meta-analyses. Diabetes Res Clin Pract. 2016;114:136-50.
46. Corona E. Mapping genetic risk of disease across the world 2016 [Available from: http://geneworld.erikcorona.com/geneworld/.
47. Marshall MC, Jr. Diabetes in African Americans. Postgrad Med J. 2005;81(962):734-40.
48. CDC. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. Atlanta: US Department of Health and Human Services; 2011.
49. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol. 2014;2(1):56-64.
50. Noble JA, Johnson J, Lane JA, Valdes AM. HLA Class II Genotyping of African American Type 1 Diabetic Patients Reveals Associations Unique to African Haplotypes. Diabetes. 2013;62(9):3292-9.
51. Ma RCW, Schmidt MI, Tam WH, McIntyre HD, Catalano PM. Clinical management of pregnancy in the obese mother: before conception, during pregnancy, and post partum. The Lancet Diabetes & Endocrinology.4(12):1037-49.
52. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. The Lancet Diabetes & Endocrinology. 2016;4(12):1025-36.
53. Federation WO. World map of obesity 2015 2015 [Available from: . http://www.worldobesity.org/resources/world-map-obesity.
54. Macaulay S, Dunger DB, Norris SA. Gestational Diabetes Mellitus in Africa: A Systematic Review. PLoS ONE. 2014;9(6):e97871.
55. Olagbuji BN, Atiba AS, Olofinbiyi BA, Akintayo AA, Awoleke JO, Ade-Ojo IP, et al. Prevalence of and risk factors for gestational diabetes using 1999, 2013 WHO and IADPSG criteria upon implementation of a universal one-step screening and diagnostic strategy in a sub-Saharan African population. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2015;189:27-32.
56. World Health Organization. Dept. of Noncommunicable Disease Surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications : report of a

WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization; 1999. 59 p. p.
57. Colagiuri S, Falavigna M, Agarwal MM, Boulvain M, Coetzee E, Hod M, et al. Strategies for implementing the WHO diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Diabetes Res Clin Pract. 2014;103(3):364-72.
58. International Association of D, Pregnancy Study Groups Consensus P, Metzger BE, Gabbe SG, Persson B, Buchanan TA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676-82.
59. Group THSCR. Hyperglycemia and Adverse Pregnancy Outcomes. New England Journal of Medicine. 2008;358(19):1991-2002.
60. Farrar D, Fairley L, Santorelli G, Tuffnell D, Sheldon TA, Wright J, et al. Association between hyperglycaemia and adverse perinatal outcomes in south Asian and white British women: analysis of data from the Born in Bradford cohort. The Lancet Diabetes & Endocrinology.3(10):795-804.
61. Hedderson M, Ehrlich S, Sridhar S, Darbinian J, Moore S, Ferrara A. Racial/ethnic disparities in the prevalence of gestational diabetes mellitus by BMI. Diabetes Care. 2012;35(7):1492-8.
62. Morrison JL, Hodgson LAB, Lim LL, Al-Qureshi S. Diabetic retinopathy in pregnancy: a review. Clinical & Experimental Ophthalmology. 2016;44(4):321-34.
63. Inkster ME, Fahey TP, Donnan PT, Leese GP, Mires GJ, Murphy DJ. Poor glycated haemoglobin control and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: Systematic review of observational studies. BMC Pregnancy and Childbirth. 2006;6(1).
64. Fraser RB. The fate of the pregnant diabetic in a developing country: Kenya. Diabetologia. 1982;22(1):21-4.
65. Huddle KR. Audit of the outcome of pregnancy in diabetic women in Soweto, South Africa, 1992 - 2002. S Afr Med J. 2005;95(10):789-94.
66. Zeck W, McIntyre HD. Gestational Diabetes in Rural East Africa: A Call to Action. Journal of Women's Health. 2008;17(3):403-11.
67. Coetzee EJ, Jackson WPU. The management of non-insulin-dependent diabetes during pregnancy. Diabetes Research and Clinical Practice. 1985;1(5):281-7.
68. Gill GV, Huddle KRL, Monkoe G. Long-term (20 years) outcome and mortality of Type 1 diabetic patients in Soweto, South Africa. Diabetic Medicine. 2005;22(12):1642-6.
69. Ekpebegh CO, Coetzee EJ, van der Merwe L, Levitt NS. A 10-year retrospective analysis of pregnancy outcome in pregestational Type 2 diabetes: comparison of insulin and oral glucose-lowering agents. Diabetic Medicine. 2007;24(3):253-8.
70. Alemu S, Dessie A, Seid E, Bard E, Lee PT, Trimble ER, et al. Insulin-requiring diabetes in rural Ethiopia: should we reopen the case for malnutrition-related diabetes? Diabetologia. 2009;52(9):1842-5.
71. Gale EAM. The Rise of Childhood Type 1 Diabetes in the 20th Century. Diabetes. 2002;51(12):3353-61.
72. Zung A, Elizur M, Weintrob N, Bistritzer T, Hanukoglu A, Zadik Z, et al. Type 1 diabetes in Jewish Ethiopian immigrants in Israel: HLA class II immunogenetics and contribution of new environment. Human Immunology. 2004;65(12):1463-8.
73. Marshall SL, Edidin D, Sharma V, Ogle G, Arena VC, Orchard T. Current clinical status, glucose control, and complication rates of children and youth with type 1 diabetes in Rwanda. Pediatric Diabetes. 2012;14(3):217-26.
74. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care. 2000;23(10):1516-26.

75. Piloya-Were T, Sunni M, Ogle GD, Moran A. Childhood diabetes in Africa. Current Opinion in Endocrinology & Diabetes and Obesity. 2016;23(4):306-11.
76. Rwiza HT, Swai ABM, McLarty DG. Failure to Diagnose Diabetic Ketoacidosis in Tanzania. Diabetic Medicine. 1986;3(2):181-4.
77. Ogle GD, Middlehurst AC, Silink M. The IDF Life for a Child Program Index of diabetes care for children and youth. Pediatric Diabetes. 2015;17(5):374-84.
78. Marshall SL, Edidin D, Arena VC, Becker DJ, Bunker CH, Gishoma C, et al. Prevalence and incidence of clinically recognized cases of Type 1 diabetes in children and adolescents in Rwanda, Africa. Diabetic Medicine. 2015;32(9):1186-92.
79. Marshall SL, Edidin DV, Arena VC, Becker DJ, Bunker CH, Gishoma C, et al. Glucose control in Rwandan youth with type 1 diabetes following establishment of systematic, HbA1c based, care and education. Diabetes Research and Clinical Practice. 2015;107(1):113-22.
80. Umpierrez GE. Narrative Review: Ketosis-Prone Type 2 Diabetes Mellitus. Annals of Internal Medicine. 2006;144(5):350.
81. WHO. National capacity to address and respond to NCDs: Existence of operational policies, strategies, or action plans 2016 [Available from: http://www.who.int/gho/ncd/health_system_response/policy_text/en/.
82. Sankoh O, Byass P. Cause-specific mortality at INDEPTH Health and Demographic Surveillance System Sites in Africa and Asia: concluding synthesis. Glob Health Action. 2014;7:25590.
83. I SATHL-AIDMTAC. Le diabète juvénile au Mali. Rev Française Endocrinol Clin Nutr Métabolisme. 1999;40:513-21.
84. Beran D, Yudkin JS, de Courten M. Access to Care for Patients With Insulin-Requiring Diabetes in Developing Countries: Case studies of Mozambique and Zambia. Diabetes Care. 2005;28(9):2136-40.
85. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N, et al. Estimated Life Expectancy in a Scottish Cohort With Type 1 Diabetes, 2008-2010. JAMA. 2015;313(1):37.
86. Bertram MY, Jaswal AV, Van Wyk VP, Levitt NS, Hofman KJ. The non-fatal disease burden caused by type 2 diabetes in South Africa, 2009. Glob Health Action. 2013;6:19244.
87. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376(9735):124-36.
88. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. The Lancet Global health. 2013;1(6):e339-49.
89. Burgess PI, MacCormick IJC, Harding SP, Bastawrous A, Beare NAV, Garner P. Epidemiology of diabetic retinopathy and maculopathy in Africa: a systematic review. Diabetic Medicine. 2013;30(4):399-412.
90. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond). 2015;2:17.
91. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. The Lancet Diabetes & Endocrinology. 2014;2(8):634-47.
92. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015;386(9995):743-800.
93. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health. 2014;2(3):e174-e81.
94. The Lancet D, Endocrinology. Diabetic kidney disease: what does the next era hold? The Lancet Diabetes & Endocrinology. 2015;3(9):665.

95. Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: A systematic review. World J Diabetes. 2015;6(5):759-73.
96. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841-5.
97. Breyer M. Faculty of 1000 evaluation for Association of trypanolytic ApoL1 variants with kidney disease in African Americans. F1000 - Post-publication peer review of the biomedical literature: Faculty of 1000, Ltd.
98. Osafo C, Raji YR, Olanrewaju T, Mamven M, Arogundade F, Ajayi S, et al. Genomic approaches to the burden of kidney disease in Sub-Saharan Africa: the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network. Kidney International. 2016;90(1):2-5.
99. Abbas Z. Chapter-04 The Global Burden of Diabetic Foot. Contemporary Management of the Diabetic Foot: Jaypee Brothers Medical Publishing; 2014. p. 24-30.
100. OJ MDMDH. Prevalence of diabetes, diabetic foot ulcer, and lower extremity amputation among Medicare beneficiaries, 2006 to 2008 Rockville2011 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK63602/.
101. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ, Schaper NC. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes/Metabolism Research and Reviews. 2016;32:2-6.
102. Cockburn N, Steven D, Lecuona K, Joubert F, Rogers G, Cook C, et al. Prevalence, Causes and Socio-Economic Determinants of Vision Loss in Cape Town, South Africa. PLoS ONE. 2012;7(2):e30718.
103. Abbas ZG, Lutale JK, Bakker K, Baker N, Archibald LK. The 'Step by Step' Diabetic Foot Project in Tanzania: a model for improving patient outcomes in less-developed countries. International Wound Journal. 2011;8(2):169-75.
104. Ndip EAA. A Study of the Prevalence and Risk Factors of Foot Problems in a Population of Diabetic Patients in Cameroon. The International Journal of Lower Extremity Wounds. 2006;5(2):83-8.
105. Ogbera AO, Fasanmade O, Ohwovoriole AE, Adediran O. An Assessment of the Disease Burden of Foot Ulcers in Patients With Diabetes Mellitus Attending a Teaching Hospital in Lagos, Nigeria. The International Journal of Lower Extremity Wounds. 2006;5(4):244-9.
106. Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. Diabetes Care. 2010;33(10):2285-93.
107. Abbas ZG, Archibald LK. Challenges for management of the diabetic foot in Africa: doing more with less. International Wound Journal. 2007;0(0):071027000841001-???
108. Abbas ZG, Lutale JK, Archibald LK. Diabetic foot ulcers and ethnicity in Tanzania: a contrast between African and Asian populations. International Wound Journal. 2009;6(2):124-31.
109. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. The Lancet. 2003;361(9368):1545-51.
110. Levitt NS, Bradshaw D, Zwarenstein MF, Bawa AA, Maphumolo S. Audit of public sector primary diabetes care in Cape Town, South Africa: high prevalence of complications, uncontrolled hyperglycaemia, and hypertension. Diabetic Medicine. 1997;14(12):1073-7.
111. Okello S, Millard A, Owori R, Asiimwe SB, Siedner MJ, Rwebembera J, et al. Prevalence of lower extremity Peripheral artery disease among adult diabetes patients in Southwestern Uganda. BMC Cardiovascular Disorders. 2014;14(1).
112. Kumar A, Mash B, Rupesinghe G. Peripheral arterial disease - high prevalence in rural black South Africans. S Afr Med J. 2007;97(4):285-8.

113. Abbas ZG, Lutale J, Archibald LK. Rodent bites on the feet of diabetes patients in Tanzania. Diabetic Medicine. 2005;22(5):631-3.
114. Dunbar GL, Hellenberg DA, Levitt N. Diabetes mellitus and non-traumatic lower extremity amputations in four public sector hospitals in Cape Town, South Africa, during 2009 and 2010. South African Medical Journal. 2015;105(12):1053.
115. Gulam-Abbas Z, Lutale JK, Morbach S, Archibald LK. Clinical outcome of diabetes patients hospitalized with foot ulcers, Dar es Salaam, Tanzania. Diabetic Medicine. 2002;19(7):575-9.
116. Lam C, Martinson N, Hepp L, Ambrose B, Msandiwa R, Wong ML, et al. Prevalence of tobacco smoking in adults with tuberculosis in South Africa. Int J Tuberc Lung Dis. 2013;17(10):1354-7.
117. Waweru P, Anderson R, Steel H, Venter WD, Murdoch D, Feldman C. The prevalence of smoking and the knowledge of smoking hazards and smoking cessation strategies among HIV-positive patients in Johannesburg, South Africa. S Afr Med J. 2013;103(11):858-60.
118. Gaziano TA. Cardiovascular Disease in the Developing World and Its Cost-Effective Management. Circulation. 2005;112(23):3547-53.
119. Addo J, Smeeth L, Leon DA. Hypertension In Sub-Saharan Africa: A Systematic Review. Hypertension. 2007;50(6):1012-8.
120. Gudina EK, Amade ST, Tesfamichael FA, Ram R. Assessment of quality of care given to diabetic patients at Jimma University Specialized Hospital diabetes follow-up clinic, Jimma, Ethiopia. BMC Endocrine Disorders. 2011;11(1).
121. Adeniyi OV, Yogeswaran P, Longo-Mbenza B, Goon DT. Uncontrolled Hypertension and Its Determinants in Patients with Concomitant Type 2 Diabetes Mellitus (T2DM) in Rural South Africa. PLOS ONE. 2016;11(3):e0150033.
122. Sobngwi E, Ndour-Mbaye M, Boateng KA, Ramaiya KL, Njenga EW, Diop SN, et al. Type 2 diabetes control and complications in specialised diabetes care centres of six sub-Saharan African countries: The Diabcare Africa study. Diabetes Research and Clinical Practice. 2012;95(1):30-6.
123. Kengne AP, Sobngwi E, Echouffo-Tcheugui J-B, Mbanya J-C. New insights on diabetes mellitus and obesity in Africa-Part 2: prevention, screening and economic burden. Heart. 2013;99(15):1072-7.
124. Kengne AP, Limen SN, Sobngwi E, Djouogo CF, Nouedoui C. Metabolic syndrome in type 2 diabetes: comparative prevalence according to two sets of diagnostic criteria in sub-Saharan Africans. Diabetol Metab Syndr. 2012;4(1):22.
125. Hertz JT, Reardon JM, Rodrigues CG, de Andrade L, Limkakeng AT, Bloomfield GS, et al. Acute Myocardial Infarction in Sub-Saharan Africa: The Need for Data. PLoS ONE. 2014;9(5):e96688.
126. Kengne AP, Amoah AG, Mbanya JC. Cardiovascular complications of diabetes mellitus in sub-Saharan Africa. Circulation. 2005;112(23):3592-601.
127. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. The Lancet Neurology. 2009;8(4):355-69.
128. Lekoubou A, Nkoke C, Dzudie A, Kengne AP. Stroke admission and case-fatality in an urban medical unit in sub-Saharan Africa: a fourteen year trend study from 1999 to 2012. J Neurol Sci. 2015;350(1-2):24-32.
129. Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. The Lancet Diabetes & Endocrinology. 2014;2(9):740-53.
130. van Crevel R, van de Vijver S, Moore DAJ. The global diabetes epidemic: what does it mean for infectious diseases in tropical countries? The Lancet Diabetes & Endocrinology.

131. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. Lancet Diabetes Endocrinol. 2016;4(2):148-58.
132. Nou E, Lo J, Hadigan C, Grinspoon SK. Pathophysiology and management of cardiovascular disease in patients with HIV. The Lancet Diabetes & Endocrinology. 2016;4(7):598-610.
133. Echouffo-Tcheugui JB, Dzudie A, Epacka ME, Choukem SP, Doualla MS, Luma H, et al. Prevalence and determinants of undiagnosed diabetes in an urban sub-Saharan African population. Primary Care Diabetes. 2012;6(3):229-34.
134. Standards of Medical Care in Diabetes--2014. Diabetes Care. 2013;37(Supplement_1):S14-S80.
135. Standards of Medical Care in Diabetes-2017: Summary of Revisions. Diabetes Care. 2017;40(Suppl 1):S4-S5.
136. Beran D, Yudkin JS. Looking beyond the issue of access to insulin: What is needed for proper diabetes care in resource poor settings. Diabetes Research and Clinical Practice. 2010;88(3):217-21.
137. Swai A. DIABETES MELLITUS MISDIAGNOSED AS AIDS. The Lancet. 1989;334(8669):976.
138. Makani J. Admission diagnosis of cerebral malaria in adults in an endemic area of Tanzania: implications and clinical description. QJM. 2003;96(5):355-62.
139. Majaliwa ES, Munubhi E, Ramaiya K, Mpembeni R, Sanyiwa A, Mohn A, et al. Survey on Acute and Chronic Complications in Children and Adolescents With Type 1 Diabetes at Muhimbili National Hospital in Dar es Salaam, Tanzania. Diabetes Care. 2007;30(9):2187-92.
140. Folb N, Timmerman V, Levitt NS, Steyn K, Bachmann MO, Lund C, et al. Multimorbidity, control and treatment of non- communicable diseases among primary healthcare attenders in the Western Cape, South Africa. South African Medical Journal. 2015;105(8):642.
141. Mash RJ, Rhode H, Zwarenstein M, Rollnick S, Lombard C, Steyn K, et al. Effectiveness of a group diabetes education programme in under-served communities in South Africa: a pragmatic cluster randomized controlled trial. Diabetic Medicine. 2014;31(8):987-93.
142. Chinenye S, Ogbera A, Fasanmade O, Ogbu O, Uloko A, Ofoegbu E, et al. Profile of Nigerians with diabetes mellitus - Diabcare Nigeria study group (2008): Results of a multicenter study. Indian Journal of Endocrinology and Metabolism. 2012;16(4):558.
143. Ogle GD, Kim H, Middlehurst AC, Silink M, Jenkins AJ. Financial costs for families of children with Type 1 diabetes in lower-income countries. Diabetic Medicine. 2015;33(6):820-6.
144. Spurling GK, Mansfield PR, Montgomery BD, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Med. 2010;7(10):e1000352.
145. Wu JHY, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. The Lancet Diabetes & Endocrinology.4(5):411-9.
146. Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. The Lancet Diabetes & Endocrinology. 2016;4(3):275-85.
147. Ogle GD, Abdullah M, Mason D, Januszewski AS, Besançon S. Insulin storage in hot climates without refrigeration: temperature reduction efficacy of clay pots and other techniques. Diabetic Medicine. 2016;33(11):1544-53.
148. Majaliwa ES, Elusiyan BE, Adesiyun OO, Laigong P, Adeniran AK, Kandi CM, et al. Type 1 diabetes mellitus in the African population: epidemiology and management challenges. Acta Biomed. 2008;79(3):255-9.

149. Basu S, Shankar V, Yudkin JS. Comparative effectiveness and cost-effectiveness of treat-to-target versus benefit-based tailored treatment of type 2 diabetes in low-income and middle-income countries: a modelling analysis. Lancet Diabetes Endocrinol. 2016;4(11):922-32.
150. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. New England Journal of Medicine. 2008;358(6):580-91.
151. Werner ME, van de Vijver S, Adhiambo M, Egondi T, Oti SO, Kyobutungi C. Results of a hypertension and diabetes treatment program in the slums of Nairobi: a retrospective cohort study. BMC Health Services Research. 2015;15(1).
152. Adedeji AR, Tumbo J, Govender I. Adherence of doctors to a clinical guideline for hypertension in Bojanala district, North-West Province, South Africa. African Journal of Primary Health Care & Family Medicine. 2015;7(1).
153. Mbanya APKAKNJC. Cardiovascular Risk Reduction in Diabetes in Sub-Saharan

Africa: What should the Priorities be in the Absence of Global

Risk Evaluation Tools. Clinical Medicine: Cardiology 2008: 2 25–31. 2008;2:25-31.
154. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of Undiagnosed Hypertension in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. Hypertension. 2014;65(2):291-8.
155. Yusuf S, Wood D, Ralston J, Reddy KS. The World Heart Federation's vision for worldwide cardiovascular disease prevention. The Lancet.386(9991):399-402.
156. Cleland CR, Burton MJ, Hall C, Hall A, Courtright P, Makupa WU, et al. Diabetic retinopathy screening: experiences from northern Tanzania. The Lancet Diabetes & Endocrinology. 2016;4(1):10-2.
157. Cleland CR, Burton MJ, Hall C, Hall A, Courtright P, Makupa WU, et al. Diabetic retinopathy in Tanzania: prevalence and risk factors at entry into a regional screening programme. Tropical Medicine & International Health. 2016;21(3):417-26.
158. Burgess PI, Msukwa G, Beare NAV. Diabetic retinopathy in sub-Saharan Africa: meeting the challenges of an emerging epidemic. BMC Medicine. 2013;11(1).
159. Matimba A, Woodward R, Tambo E, Ramsay M, Gwanzura L, Guramatunhu S. Tele-ophthalmology: Opportunities for improving diabetes eye care in resource- and specialist-limited Sub-Saharan African countries. Journal of Telemedicine and Telecare. 2015;22(5):311-6.
160. Bastawrous A, Rono HK, Livingstone IAT, Weiss HA, Jordan S, Kuper H, et al. Development and Validation of a Smartphone-Based Visual Acuity Test (Peek Acuity) for Clinical Practice and Community-Based Fieldwork. JAMA Ophthalmology. 2015;133(8):930.
161. Naicker S. Burden of end-stage renal disease in sub-Saharan Africa. Clinical Nephrology. 2011.
162. Das P, Horton R. Physical activity-time to take it seriously and regularly. Lancet. 2016;388(10051):1254-5.
163. Durao S, Ajumobi O, Kredo T, Naude C, Levitt NS, Steyn K, et al. Evidence insufficient to confirm the value of population screening for diabetes and hypertension in low- and-middle-income settings. South African Medical Journal. 2015;105(2):98.
164. Echouffo-Tcheugui JB, Mayige M, Ogbera AO, Sobngwi E, Kengne AP. Screening for hyperglycemia in the developing world: Rationale, challenges and opportunities. Diabetes Research and Clinical Practice. 2012;98(2):199-208.
165. Dalal S, Beunza JJ, Volmink J, Adebamowo C, Bajunirwe F, Njelekela M, et al. Non-communicable diseases in sub-Saharan Africa: what we know now. International Journal of Epidemiology. 2011;40(4):885-901.

166. Atun R, Aydın S, Chakraborty S, Sümer S, Aran M, Gürol I, et al. Universal health coverage in Turkey: enhancement of equity. The Lancet. 2013;382(9886):65-99.
167. WHO. Global Health Observatory country views 2016 [Available from: http://apps.who.int/gho/data/node.country.
168. WHO. Global Health Observatory Data Repository. Polices, strategies, and action plans: data by country 2016 [Available from: http://apps.who.int/gho/data/node.main.A907?lang=en.
169. Meheus DMF. Fiscal Space for Domestic Funding of Health and Other Social Services. London, UK: Chatam House; 2014.
170. State AUHo. Abuja declaration on HIV/AIDS, tuberculosis and other infectious diseases and plan of action 2001 [Available from: http://www.rollbackmalaria.org/microsites/wmd2011/abuja_declaration_final.html
171. Huffman MD, Rao KD, Pichon-Riviere A, Zhao D, Harikrishnan S, Ramaiya K, et al. A cross-sectional study of the microeconomic impact of cardiovascular disease hospitalization in four low- and middle-income countries. PLoS One. 2011;6(6):e20821.
172. Wang Q, Brenner S, Leppert G, Banda TH, Kalmus O, De Allegri M. Health seeking behaviour and the related household out-of-pocket expenditure for chronic non-communicable diseases in rural Malawi. Health Policy and Planning. 2014;30(2):242-52.
173. Wang Q, Fu AZ, Brenner S, Kalmus O, Banda HT, De Allegri M. Out-of-Pocket Expenditure on Chronic Non-Communicable Diseases in Sub-Saharan Africa: The Case of Rural Malawi. PLOS ONE. 2015;10(1):e0116897.
174. Lagomarsino G, Garabrant A, Adyas A, Muga R, Otoo N. Moving towards universal health coverage: health insurance reforms in nine developing countries in Africa and Asia. The Lancet. 2012;380(9845):933-43.
175. Alliance WGHW. A Universal Truth: No health without a workforce. Geneva: World Health Organisation; 2013.
176. Mullan F, Frehywot S, Omaswa F, Buch E, Chen C, Greysen SR, et al. Medical schools in sub-Saharan Africa. Lancet. 2011;377(9771):1113-21.
177. Scheffler RM, Mahoney CB, Fulton BD, Dal Poz MR, Preker AS. Estimates Of Health Care Professional Shortages In Sub-Saharan Africa By 2015. Health Affairs. 2009;28(5):w849-w62.
178. Mullan F, Frehywot S. Non-physician clinicians in 47 sub-Saharan African countries. The Lancet. 2007;370(9605):2158-63.
179. Celletti F, Wright A, Palen J, Frehywot S, Markus A, Greenberg A, et al. Can the deployment of community health workers for the delivery of HIV services represent an effective and sustainable response to health workforce shortages? Results of a multicountry study. AIDS. 2010;24(Suppl 1):S45-S57.
180. Mwai GW, Mburu G, Torpey K, Frost P, Ford N, Seeley J. Role and outcomes of community health workers in HIV care in sub-Saharan Africa: a systematic review. Journal of the International AIDS Society. 2013;16(1).
181. WHO. Service Availability and Readiness Assessment (SARA) [Available from: http://www.who.int/healthinfo/systems/sara_methods/en/.
182. Campbell MC, Tishkoff SA. African Genetic Diversity: Implications for Human Demographic History, Modern Human Origins, and Complex Disease Mapping. Annual Review of Genomics and Human Genetics. 2008;9(1):403-33.
183. Beran D, Silva Matos C, Yudkin JS. The Diabetes UK Mozambique Twinning Programme. Results of improvements in diabetes care in Mozambique: a reassessment 6 years later using the Rapid Assessment Protocol for Insulin Access. Diabetic Medicine. 2010;27(8):855-61.

184. Bowser D, Sparkes SP, Mitchell A, Bossert TJ, Barnighausen T, Gedik G, et al. Global Fund investments in human resources for health: innovation and missed opportunities for health systems strengthening. Health Policy and Planning. 2013;29(8):986-97.
185. WHO. WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020 Geneva; 2013.
186. Peck R, Mghamba J, Vanobberghen F, Kavishe B, Rugarabamu V, Smeeth L, et al. Preparedness of Tanzanian health facilities for outpatient primary care of hypertension and diabetes: a cross-sectional survey. The Lancet Global Health. 2014;2(5):e285-e92.
187. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. The Lancet. 2009;373(9659):240-9.
188. Mendis S. The availability and affordability of selected essential medicines for chronicl diseases in six low- and middle-income countries. Bulletin of the World Health Organization. 2007;85(4):279-88.
189. A KWS. Global trade in insulin and its public health consequences: Technical Report Health Action International. 2015.
190. MSH. International Drug Price Indicator Guide 2015 [Available from: http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=dmp&language=english
191. J BDEMLRF. Price analysis of Management Sciences for Health International Drug Price Indicator Guide: Addressing the Challenge and Constraints of Insulin Sources and Supply Study Health Action International.in press.
192. WHO. Drugs used in diabetes. 2013 [Available from: http://www.whocc.no/atc_ddd_index/?code=A10A.
193. Bank W. Global Poverty Line UPdate 2015 [Available from: http://www.worldbank.org/en/topic/poverty/brief/global-poverty-line-faq.
194. Bank W. Service Delivery Indicators Survey [Available from: http://datatopics.worldbank.org/sdi/.
195. Tudor Car L, Brusamento S, Elmoniry H, van Velthoven MHMMT, Pape UJ, Welch V, et al. The Uptake of Integrated Perinatal Prevention of Mother-to-Child HIV Transmission Programs in Low- and Middle-Income Countries: A Systematic Review. PLoS ONE. 2013;8(3):e56550.
196. Haber N, Pillay D, Porter K, Bärnighausen T. Constructing the cascade of HIV care. Current Opinion in HIV and AIDS. 2016;11(1):102-8.
197. Ali MK, Bullard KM, Gregg EW, del Rio C. A Cascade of Care for Diabetes in the United States: Visualizing the Gaps. Annals of Internal Medicine. 2014;161(10):681.
198. WHO. The STEPS Instrument and Support Materials Geneva2015 [Available from: http://www.who.int/chp/steps/instrument/en/.
199. Services NMoHaS. Namibia Demographic and Health Survey 2013. Windhoek; 2013.
200. Labadarios D, Shisana O, Rehle T, Simbayi L. SANHANES: A unique survey series in the health landscape. South African Medical Journal. 2014;104(10):675.
201. Atun R, Gale EAM. The challenge of diabetes in sub-Saharan Africa. The Lancet Diabetes & Endocrinology. 2015;3(9):675-7.
202. S BCHESVM-GJARBTV. The Global Economic Burden of Diabetes: A Cost-of-Illness Study. Mimeo. 2017.
203. Chale SS, Swai AB, Mujinja PG, McLarty DG. Must diabetes be a fatal disease in Africa? Study of costs of treatment. BMJ. 1992;304(6836):1215-8.
204. AV. N. Coût direct et indirect du diabéte en l'absence de complications chroniques a Yaoundé, Cameroun [MD]: University of Yaoundé I, Cameroon; 2002.
205. Minor T. An investigation into the effect of type I and type II diabetes duration on employment and wages. Economics & Human Biology. 2013;11(4):534-44.

206. Loeppke R, Taitel M, Haufle V, Parry T, Kessler RC, Jinnett K. Health and Productivity as a Business Strategy: A Multiemployer Study. Journal of Occupational and Environmental Medicine. 2009;51(4):411-28.
207. Seuring T, Goryakin Y, Suhrcke M. The impact of diabetes on employment in Mexico. Economics & Human Biology. 2015;18:85-100.
208. Suhrcke TSPSM. The Impact of Diabetes on Labor Market Outcomes in Mexico: A Panel Data and Biomarker Analysis. IZA; 2016.
209. Economic Costs of Diabetes in the U.S. in 2002. Diabetes Care. 2003;26(3):917-32.
210. Sharma KM, Ranjani H, Zabetian A, Datta M, Deepa M, Moses CRA, et al. Excess cost burden of diabetes in Southern India: a clinic-based, comparative cost-of-illness study. Global Health, Epidemiology and Genomics. 2016;1.
211. Esteghamati A, Khalilzadeh O, Anvari M, Meysamie A, Abbasi M, Forouzanfar M, et al. The economic costs of diabetes: a population-based study in Tehran, Iran. Diabetologia. 2009;52(8):1520-7.
212. Guariguata L, de Beer I, Hough R, Bindels E, Weimers-Maasdorp D, Feeley FG, et al. Diabetes, HIV and other health determinants associated with absenteeism among formal sector workers in Namibia. BMC Public Health. 2012;12(1).
213. Kirigia JM, Sambo HB, Sambo LG, Barry SP. Economic burden of diabetes mellitus in the WHO African region. BMC Int Health Hum Rights. 2009;9:6.
214. United Nations DoEaSA, Population Division (2015). World Populaion Prospects: The 2015 Revision, CD-ROM Edition.
215. United Nations DoEaSA, Population Division (2014). World Urbanization Prospects: The 2014 Revision, CD-ROM Edition). 2014.
216. Assah FK, Ekelund U, Brage S, Mbanya JC, Wareham NJ. Urbanization, Physical Activity, and Metabolic Health in Sub-Saharan Africa. Diabetes Care. 2011;34(2):491-6.
217. Group UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317(7160):703-13.
218. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. New England Journal of Medicine. 2009;361(10):1028-.
219. Sussman J, Vijan S, Hayward R. Using Benefit-Based Tailored Treatment to Improve the Use of Antihypertensive Medications. Circulation. 2013;128(21):2309-17.
220. Basu S, Yudkin JS, Sussman JB, Millett C, Hayward RA. Alternative Strategies to Achieve Cardiovascular Mortality Goals in China and IndiaCLINICAL PERSPECTIVE. Circulation. 2016;133(9):840-8.
221. Crampin AC, Dube A, Mboma S, Price A, Chihana M, Jahn A, et al. Profile: The Karonga Health and Demographic Surveillance System. International Journal of Epidemiology. 2012;41(3):676-85.
222. Dyslipidemia Management in Adults With Diabetes. Diabetes Care. 2003;27(Supplement 1):S68-S71.
223. WHO. Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings. 2013.
224. S I. The Yale Diabetes Center's Diabetes Facts and Guidelines, 11th edition. . New Haven: Yale Diabetes Centre; 2011.
225. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2129-43.
226. Atun RA. A framework and toolkit for capturing the communicable disease programmes within health systems: Tuberculosis control as an illustrative example. The European Journal of Public Health. 2004;14(3):267-73.

227. Atun RA, Samyshkin YA, Drobniewski F, Skuratova NM, Gusarova G, Kuznetsov SI, et al. Barriers to sustainable tuberculosis control in the Russian Federation health system2005.
228. Shigayeva A, Atun R, McKee M, Coker R. Health systems, communicable diseases and integration. Health Policy and Planning. 2010;25(Suppl. 1):i4-i20.
229. Atun RA MM, Drobniewski F, Coker R. Analysis of how health system context shapes responses to the control of human immunodeficiency virus: case studies from the Russian Federation. Bulletin of the World Health Organization. 2005;83(10):730-8.
230. Atun R, Lazarus JV, Van Damme W, Coker R. Interactions between critical health system functions and HIV/AIDS, tuberculosis and malaria programmes. Health Policy and Planning. 2010;25(Suppl. 1):i1-i3.
231. D JRLSM. Mental health reform in the Russian Federation–an integrated approach to achieve social inclusion and recovery. Bulletin of the World Health Organization. 2007;85:858-66.
232. Atun R, Pothapregada SK, Kwansah J, Degbotse D, Lazarus JV. Critical Interactions Between the Global Fund–Supported HIV Programs and the Health System in Ghana. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2011;57:S72-S6.
233. Unwin N, Mugusi F, Aspray T, Whiting D, Edwards R, Mbanya JC, et al. Tackling the emerging pandemic of non-communicable diseases in sub-Saharan Africa. Public Health. 1999;113(3):141-6.
234. Labhardt ND, Balo J-R, Ndam M, Manga E, Stoll B. Improved retention rates with low-cost interventions in hypertension and diabetes management in a rural African environment of nurse-led care: a cluster-randomised trial. Tropical Medicine & International Health. 2011;16(10):1276-84.
235. Sobry A, Kizito W, Van den Bergh R, Tayler-Smith K, Isaakidis P, Cheti E, et al. Caseload, management and treatment outcomes of patients with hypertension and/or diabetes mellitus in a primary health care programme in an informal setting. Tropical Medicine & International Health. 2013;19(1):47-57.
236. Watkins PJ. Delivering care for diabetes in Ethiopia. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999;93(4):355-6.
237. Mamo Y, Seid E, Adams S, Gardiner A, Parry E. A primary healthcare approach to the management of chronic disease in Ethiopia: an example for other countries. Clinical Medicine. 2007;7(3):228-31.
238. Katz I, Schneider H, Shezi Z, Mdleleni G, Gerntholtz T, Butler O, et al. Managing type 2 diabetes in Soweto—The South African Chronic Disease Outreach Program experience. Primary Care Diabetes. 2009;3(3):157-64.
239. Distiller LA, Brown MA, Joffe BI, Kramer BD. Striving for the impossible dream: a community-based multi-practice collaborative model of diabetes management. Diabetic Medicine. 2010;27(2):197-202.
240. Gill GV, Price C, Shandu D, Dedicoat M, Wilkinson D. An effective system of nurse-led diabetes care in rural Africa. Diabetic Medicine. 2008;25(5):606-11.
241. Price C, Shandu D, Dedicoat M, Wilkinson D, Gill GV. Long-term glycaemic outcome of structured nurse-led diabetes care in rural Africa. QJM. 2011;104(7):571-4.
242. Kengne AP, Fezeu L, Sobngwi E, Awah PK, Aspray TJ, Unwin NC, et al. Type 2 diabetes management in nurse-led primary healthcare settings in urban and rural Cameroon. Primary Care Diabetes. 2009;3(3):181-8.
243. Ndou T, van Zyl G, Hlahane S, Goudge J. A rapid assessment of a community health worker pilot programme to improve the management of hypertension and diabetes in Emfuleni sub-district of Gauteng Province, South Africa. Global Health Action. 2013;6(0).
244. D JPSPBWS. Home urinary glucose testing. Its impact on a Third World diabetic population. South African Medical Journal. 1984;65(18):731-3.

245. Pastakia SD, Karwa R, Kahn CB, Nyabundi JS. The Evolution of Diabetes Care in the Rural, Resource-Constrained Setting of Western Kenya. Annals of Pharmacotherapy. 2011;45(6):721-6.
246. Pastakia SD, Ali SM, Kamano JH, Akwanalo CO, Ndege SK, Buckwalter VL, et al. Screening for diabetes and hypertension in a rural low income setting in western Kenya utilizing home-based and community-based strategies. Globalization and Health. 2013;9(1):21.
247. Gessler N, Labhard ND, Stolt P, Manga E, Balo J-R, Boffolo A, et al. The lesson of Monsieur Nouma: Effects of a culturally sensitive communication tool to improve health-seeking behavior in rural Cameroon. Patient Education and Counseling. 2012;87(3):343-50.
248. van der Does AMB, Mash R. Evaluation of the "Take Five School": An education programme for people with Type 2 Diabetes in the Western Cape, South Africa. Primary Care Diabetes. 2013;7(4):289-95.
249. Mukama LJ, Moran A, Nyindo M, Philemon R, Msuya L. Improved glycemic control and acute complications among children with type 1 diabetes mellitus in Moshi, Tanzania. Pediatric Diabetes. 2012:n/a-n/a.
250. Windus DW, Ladenson JH, Merrins CK, Seyoum M, Windus D, Morin S, et al. Impact of a Multidisciplinary Intervention for Diabetes in Eritrea. Clinical Chemistry. 2007;53(11):1954-9.
251. Amoah AGB, Owusu SK, Acheampong JW, Agyenim-Boateng K, Asare HR, Owusu AA, et al. A national diabetes care and education programme: the Ghana model. Diabetes Research and Clinical Practice. 2000;49(2-3):149-57.
252. MakkiAwouda FO, Elmukashfi TA, Hag Al-Tom SA. Designing an Educational and Training Program for Diabetes Health Educators at Diabetic Health Centers, Khartoum State, Sudan; 2007-2010. Global Journal of Health Science. 2013;5(5).
253. Kouematchoua Tchuitcheu GB, Rienhoff O. Options for Diabetes Management in Sub-Saharan Africa with an Electronic Medical Record System. Methods of Information in Medicine. 2009;50(1):11-22.
254. Steyn K, Lombard C, Gwebushe N, Fourie JM, Everett-Murphy K, Zwarenstein M, et al. Implementation of national guidelines, incorporated within structured diabetes and hypertension records at primary level care in Cape Town, South Africa: a randomised controlled trial. Global Health Action. 2013;6(0).
255. Allain TJ, van Oosterhout JJ, Douglas GP, Joukes S, Gadabu OJ, Darts C, et al. Applying lessons learnt from the 'DOTS' Tuberculosis Model to monitoring and evaluating persons with diabetes mellitus in Blantyre, Malawi. Tropical Medicine & International Health. 2011;16(9):1077-84.
256. Govindasamy D, Kranzer K, van Schaik N, Noubary F, Wood R, Walensky RP, et al. Linkage to HIV, TB and Non-Communicable Disease Care from a Mobile Testing Unit in Cape Town, South Africa. PLoS ONE. 2013;8(11):e80017.
257. Chamie G, Kwarisiima D, Clark TD, Kabami J, Jain V, Geng E, et al. Leveraging Rapid Community-Based HIV Testing Campaigns for Non-Communicable Diseases in Rural Uganda. PLoS ONE. 2012;7(8):e43400.
258. Goudge J, Gilson L, Russell S, Gumede T, Mills A. Affordability, availability and acceptability barriers to health care for the chronically ill: Longitudinal case studies from South Africa. BMC Health Services Research. 2009;9(1).
259. Haque M, Navsa M, Emerson SH, Dennison CR, Levitt NS. Barriers to initiating insulin therapy in patients with type 2 diabetes mellitus in public-sector primary health care centres in Cape Town. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2005;10(3):94-9.
260. Hjelm K, Atwine F. Health-care seeking behaviour among persons with diabetes in Uganda: an interview study. BMC International Health and Human Rights. 2011;11(1).

261. Kolling M, Winkley K, von Deden M. "For someone who's rich, it's not a problem". Insights from Tanzania on diabetes health-seeking and medical pluralism among Dar es Salaam's urban poor. Globalization and Health. 2010;6(1):8.
262. Hansen MB, Abràmoff MD, Folk JC, Mathenge W, Bastawrous A, Peto T. Results of Automated Retinal Image Analysis for Detection of Diabetic Retinopathy from the Nakuru Study, Kenya. PLOS ONE. 2015;10(10):e0139148.
263. Dyck PJ, Overland CJ, Low PA, Litchy WJ, Davies JL, Dyck PJB, et al. Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: Cl vs. NPhys trial. Muscle & Nerve. 2010;42(2):157-64.
264. Vodopivec-Jamsek V, de Jongh T, Gurol-Urganci I, Atun R, Car J. Mobile phone messaging for preventive health care. Cochrane Database of Systematic Reviews: Wiley-Blackwell; 2012.
265. Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for communicating results of medical investigations. Cochrane Database of Systematic Reviews: Wiley-Blackwell; 2012.
266. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging telemedicine for facilitating self management of long-term illnesses. Cochrane Database of Systematic Reviews: Wiley-Blackwell; 2008.
267. R CJG-UIdJTV-JVA. Mobile phone messaging reminders for attendance at healthcare appointments. cochrane database of systematic reviews. 2012.
268. van Velthoven MHMMT, Car LT, Car J, Atun R. Telephone Consultation for Improving Health of People Living with or at Risk of HIV: A Systematic Review. PLoS ONE. 2012;7(5):e36105.
269. Gill GV, Yudkin JS, Keen H, Beran D. The insulin dilemma in resource-limited countries. A way forward? Diabetologia. 2010;54(1):19-24.
270. Atun R, Jaffar S, Nishtar S, Knaul FM, Barreto ML, Nyirenda M, et al. Improving responsiveness of health systems to non-communicable diseases. The Lancet. 2013;381(9867):690-7.
271. Fraser HSF, Allen C, Bailey C, Douglas G, Shin S, Blaya J. Information Systems for Patient Follow-Up and Chronic Management of HIV and Tuberculosis: A Life-Saving Technology in Resource-Poor Areas. Journal of Medical Internet Research. 2007;9(4):e29.
272. Shiferaw F, Zolfo M. The role of information communication technology (ICT) towards universal health coverage: the first steps of a telemedicine project in Ethiopia. Global Health Action. 2012;5(0).
273. Kahn JG, Yang JS, Kahn JS. 'Mobile' Health Needs And Opportunities In Developing Countries. Health Affairs. 2010;29(2):252-8.
274. Chandrasekhar CP, Ghosh J. Information and communication technologies and health in low income countries : the potential and the constraints2001.
275. Atun R, de Jongh T, Secci F, Ohiri K, Adeyi O. Integration of targeted health interventions into health systems: a conceptual framework for analysis. Health Policy and Planning. 2009;25(2):104-11.
276. Atun R. Health systems, systems thinking and innovation. Health Policy and Planning. 2012;27(suppl 4):iv4-iv8.
277. van Olmen J, Schellevis F, Van Damme W, Kegels G, Rasschaert F. Management of Chronic Diseases in Sub-Saharan Africa: Cross-Fertilisation between HIV/AIDS and Diabetes Care. Journal of Tropical Medicine. 2012;2012:1-10.
278. Schouten EJ, Jahn A, Midiani D, Makombe SD, Mnthambala A, Chirwa Z, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. The Lancet. 2011;378(9787):282-4.

279. WHO. NCD Global Monitoring Framework [Available from: http://www.who.int/nmh/global_monitoring_framework/en/.
280. Popkin BM, Hawkes C. Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses. The Lancet Diabetes & Endocrinology. 2016;4(2):174-86.
281. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, et al. Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes. New England Journal of Medicine. 2009;361(1):40-51.
282. Nations U. Declaration of Commitment on HIV/AIDS. Global Crisis — Global Action [Available from: http://www.un.org/ga/aids/coverage/FinalDeclarationHIVAIDS.html.
283. Jobanputra K, Boulle P, Roberts B, Perel P. Three Steps to Improve Management of Noncommunicable Diseases in Humanitarian Crises. PLoS Med. 2016;13(11):e1002180.
284. Nations U. Political declaration of the high-level meeting of the General Assembly on the prevention and control of non-communicable diseases 2011 [Available from: http://www.un.org/ga/search/view_doc.asp?symbol=A/66/L.1.
285. Nations U. Resolution Adopted By The General Assembly On 13 May 2010. 64/265. Prevention And Control Of Non-Communicable Diseases 2010 [Available from: http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/64/265&Lang=E.
286. WHO. Sixty-fifth World health Assembly. A/65/54. Second report of the Committee A. [Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_54-en.pdf
287. Atun R. Decisive action to end apathy and achieve 25×25 NCD targets. The Lancet. 2014;384(9941):384-5.
288. Moon S, Sridhar D, Pate MA, Jha AK, Clinton C, Delaunay S, et al. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. The Lancet. 2015;386(10009):2204-21.
289. Evans T, Nishtar S, Atun R, Etienne C. Scaling up research and learning for health systems: time to act. The Lancet. 2008;372(9649):1529-31.
290. George PP, Papachristou N, Belisario JM, Wang W, Wark PA, Cotic Z, et al. Online eLearning for undergraduates in health professions: A systematic review of the impact on knowledge, skills, attitudes and satisfaction. Journal of Global Health. 2014;4(1).
291. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database of Systematic Reviews: Wiley-Blackwell; 2012.
292. Global Economic Prospects, January 2015. Global Economic Prospects: The World Bank; 2015.
293. Atun R, Knaul FM, Akachi Y, Frenk J. Innovative financing for health: what is truly innovative? The Lancet. 2012;380(9858):2044-9.
294. Atun R, Silva S, Ncube M, Vassall A. Innovative financing for HIV response in sub–Saharan Africa. Journal of Global Health. 2016;6(1).
295. Fitchett JR, Fan Li J, Atun R. Innovative financing for late-stage global health research and development: the Global Health Investment Fund. International Health. 2015:ihv067.