INTRODUCTION
The eight-millennium development goals (MDG’s) to be achieved by year 2015 comprised of three health related goals, namely MDG4, MDG5 and MDG6 out of eight. It was MDG6, which pertained to combating AIDS, malaria and other diseases such as tuberculosis. However the MDG’s failed to address an issue of immense public health concern, i.e., the non-communicable diseases (NCD’s). This becomes even more pertinent to tackle given the burgeoning epidemic of chronic diseases without the subsequent decrease of infectious diseases, which provides opportunities for interaction between diseases not seen previously leading to significant public health consequences.

This confluence of the epidemics of communicable diseases (CD’s) and NCD’s was not foreseen by Omran when he put forward the epidemiological transition theory of receding pandemics followed by an age of degenerative diseases. However, as we enter year 2016, we see the replacement of these eight MDG’s by the 17 sustainable development goals (SDG’s) comprising of 169 targets. It is SDG number 3 relating to ensuring healthy lives and promoting well-being for all at all ages, which addresses both communicable and non-communicable diseases in its targets 3.3 and 3.4 stated as “by 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases” and “by 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being” respectively.

Today, with the global increase in the diabetic population there is a resurgence of interest in the dual epidemic of diabetes mellitus (DM) and tuberculosis (TB), which has a bidirectional detrimental relationship with negative consequences for co-infected patients. Pakistan is feared to be hit the hardest, occupying fifth position amidst the 22 high burden TB countries, and ranking seventh in the global diabetic burden. The diabetes tuberculosis treatment outcome (DITTO) study was undertaken to determine the impact of diabetes on tuberculosis treatment outcome in Pakistan. The generation of such scientific evidence is useless if it is not utilized for policy making and practice, especially in a developing country like ours with a dearth of resources. In this paper, we have developed a framework for the transfer of scientific evidence regarding the impact of diabetes on TB treatment outcomes into policy and practice. The framework is divided into three components namely; generation of scientific evidence harnessing international and national efforts, informing health policy and practice and addressing other concerns such as social protection, health education and future research.

Keywords: Tuberculosis; diabetes, co-infection, treatment outcome, policy to practice
systems, for the equitable distribution of scarce resources and for combating communicable and non-communicable diseases (NCDs). Once this evidence is generated, it needs to be used in evidence based policy making and practices for improved health outcomes. The process of policy making has various stages. These include agenda setting, formulation, implementation and evaluation, each with distinct evidence requirements which are evidence regarding the magnitude of a problem, evidence regarding policy options and one best option in terms of expected cost and outcome of an intervention, operational evidence for further enhancement of an intervention and evidence for monitoring and evaluation respectively.12

In this paper, we have developed a framework for the transfer of scientific evidence regarding the impact of diabetes on TB treatment outcomes into policy and practice. This synthesizes results of the DITTO study, various related literatures of diabetes-tuberculosis co-infection and treatment outcomes, of policy to practice, and the end TB strategy and the collaborative framework for care and control of Tuberculosis and Diabetes developed by WHO and the International Union Against Tuberculosis and Lung Disease’s (IUATLD) in 2011. The framework (Figure-1), which follows has three main components:

1). Generation of scientific evidence harnessing international and national efforts
2). Informing health policy and practice
3). Addressing other concerns: social protection, health education and future research

**Generation of Scientific Evidence**

It is known that health policy making rarely utilizes scientific evidence in the policy making process. Hence, health benefits are not accrued by those who deserve them the most; leading to ineffective, inefficient and inequitable health systems.13 This at times arises due to the lack of availability of relevant scientific evidence. It is of paramount importance to generate scientific evidence regarding the impact of diabetes on TB treatment outcomes through research to inform health policy makers. This enables them to make informed decisions aimed at improvement of the health of the population, especially in developing countries with scarce resources.14

**Global and Regional Evidence**

One source of scientific evidence used to inform policy and practice includes systematic reviews and meta-analysis. Systematic reviews synthesize research that is conducted globally. This global evidence provides us with a starting point regarding the effect of various policies and programmes.13,15 The systematic review conducted by Baker et al to see the effect of diabetes on tuberculosis treatment outcome showed adverse treatment outcome among diabetic patients undergoing treatment for tuberculosis. The risk of death, relapse and combined failure and death was more among the diabetic tuberculosis patients as compared to the non-diabetic tuberculosis patients.16

The collaborative framework for care and control of Tuberculosis and Diabetes proposed by IUATLD and WHO in 2011 identified screening patients of TB for DM and patients of DM for TB as a high priority research question.17 India is also faced with an evolving burden of diabetes and has an existing high magnitude of TB. They undertook pilot projects of screening TB patients for diabetes within their routine health care practices. This has led them to formulate policy directive for all patients registered with TB control program to undergo screening for DM. Additionally, they have integrated the functioning of their NCD and TB control programs for optimum outcome.18

This bi-directional screening was also piloted in China, where it was found feasible.19 China and India screen DM patients for TB with the help of a symptom based questionnaire. Patients thus suspected of TB are referred for further investigation.20 Screening diabetics for TB would help identify and initiate timely treatment of TB patients, reducing the risk of transmission and also better care and control of diabetes.21 Additionally screening of TB patients for DM will help identify the undiagnosed cases of diabetes and bring them into the health care system for management to prevent or delay diabetic associated complications and improve TB treatment outcomes.

**Local Evidence**

In order to inform policy and practice research needs to be conducted locally as well, by credible researchers, using appropriate methods to generate valid, unbiased and high quality evidence. This contextual and timely undertaking of research is necessary to inform the policy making process.13,15 The DITTO study was undertaken in Pakistan, which aimed to estimate the risk of adverse outcomes in diabetic patients who were being treated for tuberculosis. The study endeavoured to generate quality scientific evidence based on its prospective cohort design, taking into account potential confounders, and ascertainment of patients’ diabetic status employing fasting and random blood glucose tests and using standardized treatment outcome definitions provided by WHO. The DITTO study reported that diabetic TB patients were more likely to experience an unfavourable treatment outcome and had a decreased survival as compared to non-diabetic TB patients. Other researchers have also documented this poor treatment outcome among diabetic PTB patients.22 Diabetes needs to be addressed to prevent TB and optimize treatment outcome among TB patients. Similarly, TB needs to be timely diagnosed and appropriately treated, as it can worsen glycaemic control and clinical management of diabetes. This co-morbidity is also seen to impede the attainment of WHO 2035 targets for TB incidence and mortality.23 The global and local evidence generated till now underscores the need to co-manage DM and TB.
Inform health policy and practice

Dissemination of Research Results and Advocacy

In order to inform policy and practice research findings need to be communicated using various methods to all stakeholders. These methods include disseminating research results at conferences, seminars, and workshops and through publication in scientific journals, through media involvement, through meetings with program planners and implementers and developing policy briefs. Active engagement with concerned individuals and advocating for improved outcome among DM and DM-PTB patients.
TB co-infected individuals is required for better utilization of research.\textsuperscript{24} The research findings thus disseminated should be in a format that is simple and comprehensible by the policy makers containing targeted messages in non-academic language.

**Engagement of Stakeholders**

The involvement of various stakeholders in all stages of research proves beneficial in adoption of research results into policy and practice.\textsuperscript{25} Stakeholder involvement should ideally begin from inception of a research process to its completion. The decision on the range of stakeholders to be involved depends upon the research topic under consideration.\textsuperscript{26} The stakeholders in our context include: Health Ministry, donors, community members, private and public physicians, program heads of communicable and non-communicable disease control in the country and beneficiaries of the program. In Pakistan, for the communicable disease TB, a well-established NTP exists, whereas, for the non-communicable disease DM no established program exists. Although, Pakistan was the first developing country to have formulated the “National Action Plan for the Prevention and Control of Non-communicable disease and Health Promotion in Pakistan” but this plan could not be implemented.\textsuperscript{27} However, various organizations such as the Diabetic Association of Pakistan (DAP), Pakistan Diabetes Mellitus Prevention Program, Pakistan Diabetes Leadership forum and National Association of Diabetes Educators in Pakistan (NADEP), are working on various aspects of diabetes prevention and control. Hence they should be taken on board.

**Co-management of DM and TB**

A comprehensive and integrated program for the co-management of both diseases needs to be planned and initiated considering the negative effect of DM on TB having implications for the individual in terms of poor treatment outcome and for the family and community through increased chances of secondary transmission and greater risk of TB incidence. We also need to establish referral processes for patients of TB diagnosed with DM and for the DM patients diagnosed with TB. DITTO study noted that most diabetic PTB patients didn’t go for consultation to a diabetic consultant when they were referred to one for free management of their diabetes. This could be attributed to non-availability of resources such as transport, money and time. However, the lack of knowledge regarding the impact of co-morbidity on treatment outcome may be a contributing factor, which needs to be addressed.

**Operational Research (Bi-directional screening)**

We propose that Pakistan also institute measures taken by China and India to combat this co-epidemic of DM and TB. We recommend bi-directional screening should be conducted to control the double burden of disease prevalent in our country. A national stakeholder meeting should be conducted to build consensus on DM-TB co-management and the requirement for generation of high quality scientific evidence by conducting operational research. Operational research will help find out how best to implement such activities. Pilot projects sites need to be identified and protocols developed for screening patients for diabetes. All TB patients should undergo screening for DM using a pre-determined protocol and vice versa. Additionally, training of health workers and recording and reporting of study results needs to be sorted out. All this needs to be documented in an operations protocol. At the end, all activities including the challenges faced during the study need to be documented to guide future scaling up procedure.\textsuperscript{28}

**Other Concerns:**

**Social Protection**

Global consensus exists regarding provision of social protection to TB patients in addition to prevention and control services.\textsuperscript{29} The Prime Ministers National Health Program was initiated in 17 districts of Pakistan on 31\textsuperscript{st} Dec. 2015. It is the first health insurance program of the country, which includes free treatment for patients of various diseases including diabetes mellitus.\textsuperscript{30} It is recommended that TB patients should also be included in the National social protection programs. The DITTO study observed that majority of TB patients belong to poor households and some do not have the money to spend on transport to the health facility. This hinders their uninterrupted ATT consumption. Considering the physical and mental burden of co-infection among diabetic-PTB patients it is imperative that they be included in social protection networks; to address their economic burden. Also safe guarding TB patients from catastrophic health spending is an important component of the end TB strategy.\textsuperscript{31}

**Health Education**

The co-infected patients, their family members and communities need to be educated regarding the effect of each disease on the other. In addition to prevention and control measures against TB they need to be told about the importance of compliance with ATT, consumption of anti-diabetic medications, frequent visits to diabetic physician, monitoring of glycaemic control and maintaining an optimum weight.\textsuperscript{32}

**Future Research**

**Therapeutic Options**

Additionally, physicians treating diabetic TB patients need to keep in mind that the anti-tuberculosis drug Rifampicin has an impact on the level of anti-diabetic medicines. Therefore, it is suggested that diabetic TB patients’ glycaemic control be monitored during
ATT, they may be switched to metformin, whose metabolism is not affected by ATT given the patient tolerates the drug and also switching to insulin therapy instead of oral hypoglycaemic agents. The diabetic TB patients are treated using CAT-1 ATT regimen analogous to non-diabetic TB patients. As antidiabetic drugs have no impact on anti-tuberculosis treatment, nevertheless the dose of Rifampicin, which is 10 mg/Kg body weight may need adjustment for diabetic TB patients who in addition to being overweight at treatment initiation also tend to gain weight as the treatment for TB progresses. And it is known that the action of Rifampicin is dose dependent, the levels of which were found to be 50% lower among heavier diabetic TB patients according to an Indonesian study. Some researchers have also suggested to increase the duration of treatment for co-infected patients beyond the prescribed six-month regimen. However, supporting evidence is not of high quality. Thus there is a need to undertake research in the future to find optimum treatment strategies.

Glycaemic Control
It is speculated that good glycaemic control in diabetic patients with TB will benefit patients and hence needs to be given priority. The DITTO study was unable to study the effect of glucose control on TB treatment outcome as HbA1c values for the entire cohort were not available. Due to resource constraints glycosylated haemoglobin blood analyses was performed of only the diabetics in the study. Researchers have postulated that a better control of diabetes among tuberculosis patients will improve treatment outcomes. We recommend studies need to be conducted in the future to look at the effect of glycaemic control on TB treatment outcomes. If treatment outcome among diabetic PTB patients is modified by glucose control, then the most effective approach to achieving glycaemic control has to be determined.

CONCLUSION
Given the existing high burden of tuberculosis patients and the swelling numbers of diabetics in the country, with global and local evidence of bi-directional detrimental interaction between the two diseases the time to act is now. Generation of scientific evidence without its consumption by policy makers is a futile activity. Using appropriate dissemination channels and involvement of stakeholders in the research process increases the chances of evidence-based policy making and practice. A holistic, comprehensive and integrated program to manage TB and DM needs to be initiated, initially by adopting bi-directional screening to identify TB among DM patients and DM among TB patients and bringing them into the health care system for appropriate management. However, more research and evidence is required to determine optimum therapeutic options for co-infected individuals, effect of glycaemic control on TB treatment outcome and developing an integrated mechanism to cater for the needs of newly diagnosed diabetics and tuberculosis patients.

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