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Screening for Type 2 Diabetes

Report of a World Health Organization and International Diabetes Federation meeting

World Health Organization

Department of Noncommunicable Disease Management

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1 Introduction

Over the past decade it has been obvious that the prevalence of type 2 diabetes is increasing rapidly. Unless appropriate action is taken, it is predicted that there will be at least 350 million people in the world with type 2 diabetes by the year 2030. This is double the current number. Equally alarming and less well known is the fact that, of these people, only around one half are known to have the condition. This has been shown repeatedly in epidemiological surveys. An added concern is that half of those who do present with type 2 diabetes clinically already have signs of the complications of the disorder.

It has not yet been proven that earlier detection will improve the outcome of people with type 2 diabetes, but it seems logical to suggest that it may help. The implication of this is that people need to be screened for diabetes on a regular basis. There is still uncertainty whether this should be done on a population-wide basis or just for those people who can be shown to have a high risk. It is also uncertain at what age the screening programmes should be introduced, if at all.

This report focuses solely on screening for type 2 diabetes in non-pregnant adults. It does not consider screening for type 1 diabetes, screening for type 2 diabetes in children, nor screening for gestational diabetes. This is not to imply that these topics are unimportant. On the contrary, they are each important enough to require detailed consideration in their own right.

It is clear to both the World Health Organization (WHO) and the International Diabetes Federation (IDF) that guidance is needed for both our member countries and member associations. Because of this the WHO and the IDF have come together to produce this document, which, though it poses as many questions as it answers, is a clear and logical start to a very serious debate. We hope that the report will provide guidance and provoke discussion and new studies and in the long term will be of benefit to the many people in the world with and at risk of type 2 diabetes.

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2 Background

2.1 Diabetes and its consequences

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[1]. The current diagnostic criteria are shown in Table 1 In summary, diabetes is diagnosed if the (venous) fasting plasma glucose (FPG) value is >= 7.0 mmol l^{-1} (126 mg dl^{-1}), or if the casual plasma glucose value is >= 11.1 mmol l^{-1} (200 mg dl^{-1}), or if the plasma glucose value 2 hours after a 75g oral load of glucose >= 11.1 mmol l^{-1} (200 mg dl^{-1}). In asymptomatic subjects, performing the test on one occasion is not enough to establish the diagnosis (i.e. basis to treat diabetes). This must be confirmed by carrying out at least one further test on a subsequent day.

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are risk categories for the future development of diabetes and cardiovascular disease (CVD). An individual falling into the IFG category on the fasting result may also have IGT on the 2-h value or, indeed, diabetes. If an individual falls into two different categories, the more severe one applies.

The classification of diabetes is based on aetiological types[1]. Type 1 indicates the processes of beta-cell destruction that may ultimately lead to diabetes in which insulin is required for survival. Type 2 diabetes is characterized by disorders of insulin action and /or insulin secretion. The third category, "other specific types of diabetes," includes diabetes caused by a specific and identified underlying defect, such as genetic defects or diseases of the exocrine pancreas.

The latest WHO Global Burden of Disease estimates the worldwide burden of diabetes in adults to be around 173 million in the year 2002 [3]. Around two thirds of these live in developing countries. Diabetes is no longer a condition of developed, ‘industrialised’ or ‘Western’ countries. Global estimates of the burden of IFG and IGT are not available, but the number of people with IGT is likely to be even greater than the number with diabetes[4,3]. IGT and IFG are now sometimes referred to as ‘pre-diabetes’ (a term not unanimously supported by those attending this meeting since diabetes will not necessarily develop in those with IGT or IFG).

The diabetes epidemic is accelerating in the developing world, with an increasing proportion of affected people in younger age groups. Recent reports describe type 2 diabetes being diagnosed in children and adolescents[5,6,7]. This is likely to increase further the burden of chronic diabetic complications worldwide.

Most of the consequences of diabetes result from its macrovascular and microvascular complications. (Some describe a third category – 'neuropathic', whereas others classify the diabetic neuropathies as microvascular complications.) The age-adjusted mortality, mostly due to coronary heart disease (CHD) in many but not all populations, is 2-4 times higher than in the non-diabetic population[8], and people with diabetes have a 2-fold increased risk of stroke[9]. Diabetes is the leading cause of end stage renal failure in many populations in both developed and developing countries[10]. Lower extremity amputations are at least 10 times more common in people with diabetes than in non-diabetic individuals in developed countries[11], and more than half of all non-traumatic lower limb amputations are due to diabetes. In developed countries, diabetes is one of the leading causes of visual impairment and blindness[12,13].

People with diabetes require at least 2-3 times the health care resources of people who do not have diabetes, and diabetes care accounts for up to 15% of national healthcare budgets[14,15].

2.2 Screening for type 2 diabetes – why WHO and IDF convened this meeting

The main reasons for the current interest in screening for type 2 diabetes and the reasons why WHO and IDF convened this meeting are:

- that there is a long, latent, asymptomatic period in which the condition can be detected[16,17];
- a substantial proportion of people with type 2 diabetes are undiagnosed (Table 2);
- a substantial proportion of newly referred cases of type 2 diabetes already have evidence of the micro-vascular complications of diabetes[18];
- the rising prevalence[19] of type 2 diabetes world-wide;
- the seriousness of the immediate effects and long-term complications of type 2 diabetes;
- evidence supporting the efficacy of intensive blood glucose control[20,21] blood pressure control[22] and blood lipid control[23,24 , 25,26] in type 2 diabetes and
- accumulating evidence that treatment of hypertension, dyslipidaemia (for example lowering LDL cholesterol[23,24]) can prevent cardiovascular disease in people with type 2 diabetes.

- increasing pressure from professional organisations, lay groups and from some of the member associations of IDF to institute screening for type 2 diabetes if only to further highlight the increasing prevalence and public health importance of the condition.

requests from national and regional health authorities and individual health care professionals for guidance as to what should be their policies for screening for type 2 diabetes.

2.3 Effects of screening on individuals, health systems and society

Policies and practices for screening for type 2 diabetes have profound implications for individuals, health systems and society as a whole. Implications for individuals include:

- the time and other resources necessary to undergo the screening test (or tests) and any subsequent diagnostic test (or tests);

- the psychological and social effects of the results whether the screening test proves 'positive' or 'negative' and whether or not the diagnosis of type 2 diabetes is subsequently made and

- the adverse effects and costs of earlier treatment of type 2 diabetes or of any preventive measures instituted as a result of the individual being found to have diabetes. These may include occupational discrimination and/or increased costs or difficulty in obtaining insurance.

The effects on the health system and society as a whole are:

- the costs and other implications (especially in primary care and support services such as clinical biochemistry) of carrying out the screening test (or tests) and the necessary confirmatory test (or tests);

- the additional costs of the earlier treatment of those found to have diabetes or to be at high risk of developing diabetes or cardiovascular disease in the future and

- the implications of false negative and false positive results which are inevitable given that any initial test will be a screening test and not a full diagnostic test (except in the case of an OGTT with markedly abnormal values).

- any loss of production as a result of the earlier diagnosis of the condition (from absence from work or reduced job opportunities, for example).

The potential benefits of early detection of type 2 diabetes are:

- enhanced length and/or quality of life which might result from a reduction in the severity and frequency of the immediate effects of diabetes or the prevention or delay of its long-term complications.

- Any saving or redistribution of health care resources which might be possible as a result of reduced levels of care required for diabetes complications (reduced hospital admissions and lengths of stay etc.).

2.4 Screening and prevention - the links

Any programme aimed at the early identification of type 2 diabetes through screening will also identify individuals with IGT and/or IFG. Thus any policy, whether related to public health or day-to-day clinical practice must specify what should be done when these conditions are identified.

The prognostic significance of IGT and, to an extent IFG, is being clarified[27]. Also, evidence concerning the effect of interventions in IGT is now available. In particular, interventions aimed at weight reduction and increased physical activity and the use of some pharmacological agents have been shown to be effective in reducing or delaying the transition to diabetes in those with IGT.

In general, lifestyle interventions appear to be more effective than medications[28] and the most important, recent trials published in peer reviewed journals are summarised in Table 3.

The Diabetes Prevention Programme (DPP) Research Group evaluated the cost-effectiveness of the interventions used in their trial[29]. Life-style intervention and metformin were both judged to be cost-effective. The lowest value for cost per QALY gained (from the health system perspective) was USD 8,100. This was for the comparison of lifestyle changes with placebo, with lifestyle advice given as it might be in routine clinical practice (i.e. less intensively) – to groups of 10 patients - and with the optimistic assumption that there would be no reduction in clinical effectiveness. The highest cost per QALY was USD 99,600. This related to the comparison of metformin with placebo, as implemented in the DPP trial (i.e. with individual clinical care). The equivalent costs per QALY gained from the societal perspective were USD 23,800 and USD 99,200.

Within the context of the US these were judged to be cost-effective. In health care systems with lower staff and/or medication costs these costs per QALY would be lower and the interventions, all other things being equal, would be more cost-effective.

Given this new, encouraging information on the prevention of or delay in the transition from IGT to diabetes, there is at least potential benefit from the detection of this condition through screening. Whether similar benefits will follow from the early detection of diabetes is another issue.

3 Aims of the meeting

The aims of this WHO/IDF meeting were:

- To review the scientific evidence for the usefulness of screening for early detection of type 2 diabetes.
- To make recommendations relevant to health care policy, action and future research.
- To explain these recommendations in a joint WHO/IDF Report.

4 Terminology – what is screening?

The Group's working definition of the term **screening** is based on that used in the WHO "Principles of Screening" document[30] (September 2001 draft):

"Screening is the process of identifying those individuals who are at sufficiently high risk of a specific disorder to warrant further investigation or direct action."

The definition goes on to say:

"It [screening] is systematically offered to a population of people who have not sought medical attention on account of symptoms of the disease for which screening is being offered and is normally initiated by medical authorities and not by a patient's request for help on account of a specific complaint. The purpose of screening is to benefit the individuals being screened."

The term **diagnosis** refers to confirmation of diabetes in people who have symptoms, or who have had a positive screening test. In diabetes, the screening test may be the diagnostic test (e.g. a fasting plasma glucose => 7.0 mmol l^{-1} in someone who has symptoms) or the first part of the diagnostic test if a second test (usually the OGTT) is used to confirm the diagnosis in asymptomatic individuals.

There are several potential approaches to screening for diabetes:

- **Screening the entire population** (never actually suggested since all proposals have been, in some way, selective).

- **Selective or targeted screening** performed in a subgroup of subjects who have already been identified as being at relatively high risk in relation to age, body weight, ethnic origin etc.

- **Opportunistic screening** carried out at a time when people are seen, by health care professionals, for a reason other than the disorder in question.

'Selective or targeted screening' and 'opportunistic screening' are not mutually exclusive since screening may be limited to those at highest risk. In opportunistic screening, the decision to initiate the health care encounter is made by the individual, albeit for reasons not related to the condition for which screening is offered. This needs to be distinguished from screening programmes in which the invitation to come forward and be screened is part of the programme.

There is also 'haphazard' screening, characterised by a lack of a coherent screening policy. In such cases individuals may be invited to be screened irrespective of their risk (people in a supermarket, for example) or there may be no adequate explanation of the reasons for screening or no formal system of support for those taking part, whatever the outcome of their test.

5 Evaluating screening tests and programmes

5.1 General issues

The **sensitivity** of a screening test is the proportion of people with the disorder who test positive on the screening test. (A highly sensitive screening test is unlikely to miss a subject with diabetes.)

The **specificity** of a screening test is the proportion of people who do not have the disorder who test negative on the screening test. (A highly specific test is unlikely to misclassify someone who does not have diabetes as having diabetes.)

Although it is desirable to have a test that is both highly sensitive and highly specific, this is usually not possible. In choosing a cut-off point a trade-off needs to be made between sensitivity and specificity, since increasing one reduces the other. The receiver operator characteristic (ROC) curve expresses this relationship. The true positive rate (sensitivity) is plotted on the y axis against the false positive rate (1-specificity) over a range of cut-off values. Tests that discriminate well crowd toward the upper left corner of the ROC curve (Figure 1). In ideal cases, as sensitivity increases, there is little decrease in specificity, until very high levels of sensitivity are reached[31].

What should happen, in practice, is that ROC curves should be used in conjunction with pre-specified performance indicators (such as the proportion of cases that should be identified, what proportion of re-tests are acceptable). Some measure of 'trade-off' between performance indicators is likely to be necessary.

Validity is the extent to which the test reflects the true status of the individual.

Reliability is the degree to which the results obtained by any given procedure can be replicated.

Reproducibility refers to obtaining similar or identical results on repeated measurements on the same subject.

Screening tests must be shown to be valid, reliable and reproducible in the population in which screening is to take place. Uniform procedures and methods, standardized techniques, properly functioning equipment, and quality assurance are all necessary to ensure reliability and reproducibility.

Predictive value relates to the probability that a person has or does not have the disorder given the result of the test. Thus:

> **Positive predictive value** is the probability of the disorder in a person with a positive test result and **negative predictive value** is the probability of a person not having the disorder when the test result is negative.

The predictive value of a test is determined not only by the sensitivity and the specificity of the test, but also by the prevalence of the disorder in the population being screened. Thus, a highly sensitive and specific test will have a high positive predictive value in a population with a high prevalence of the disorder. This is part of the rationale for promoting selective or targeted screening. When the prevalence is low, as may be the case when the entire population (or the entire adult population) is screened, then the positive predictive value of the same test will be considerably lower. In this case, a high specificity drives a high positive predictive value. To avoid false positives (throughout the range of prevalence) it may be necessary to increase specificity at the expense of sensitivity.

Screening tests may be used **in parallel** (i.e. a person is deemed to be likely to have a disorder if they test positive to *either* test). In this case the sensitivity and the negative predictive value are generally increased and the specificity and positive predicted values decreased.

On the other hand, screening tests may be used **in series** (i.e. a person needs to be positive to *both* tests in order to be deemed likely to have the disorder). In this case the specificity and positive predicted value

are generally increased and the sensitivity and negative predicted value decreased. Tests in series have been advocated in type 2 diabetes (this is further discussed below) when, for example, a questionnaire may precede a fasting blood sample or OGTT and be used to exclude some individuals deemed to be at low risk of having the disorder.

5.2 Issues specific to diabetes

5.2.1 Range of available tests

Screening tests for type 2 diabetes include **risk assessment questionnaires**, **biochemical tests** and c**ombinations** of the two. The biochemical tests currently available are blood glucose or urine glucose measurements, blood HbA_{1c} or blood fructosamine measurements. Each screening test needs a designated and pre-determined threshold or 'cutpoint' that defines high risk. Screening tests are usually followed by diagnostic tests (fasting plasma glucose (FPG) and/or an oral glucose tolerance test (OGTT) using standard criteria) in order to make the diagnosis.

5.2.2 Evaluating screening procedures

Meaningful evaluation and comparison of the performance of screening tests and procedures for diabetes should be carried out against specified criteria and should take into account the following basic principles:

- People with known diabetes should not be included in the prevalence data used to calculate PPV
- Selection of cut-off points:
    - should ideally be determined using ROC curve analysis because this considers performance over the whole range of cutpoints
    - alternatively these can be determined by using a common specificity or sensitivity
    - should take into account the aims of the screening programme, available resources to meet the workload which will be generated by the proportion of the population which will require further testing, and the importance placed on avoiding false positive and false negative results
- A valid assessment of screening tests requires the whole screened population (or a sample of them) to have diagnostic testing, not just those who screen positive
- Performance should be validated on a population different to that from which the screening procedure was developed

- A distinction should be made between an *epidemiological* and a *clinical* diagnosis of diabetes. An epidemiological diagnosis can be based on a single OGTT or FPG whereas a clinical diagnosis, in the absence of symptoms, requires confirmation by a repeat test.
- The precisely specified objectives of the programme.

5.2.3 Performance indicators

A standard set of performance indicators should be used to evaluate a screening procedure or test and include: statistical performance (sensitivity, specificity, PPV, ROC - area under the curve) and the percentage of the population identified which requires further or definitive testing. Additional indicators include information on the cardiovascular disease risk profiles of identified individuals and measures of the economic performance of screening tests and population measures such as the acceptability of the screening programme to those invited to attend, the extent to which any lack of acceptability reduces uptake, the psychosocial impact of each screening outcome – positive and negative, 'true' and 'false' and the ability of those found to be at risk of future development of diabetes to modify these risk

5.2.4 Performance of screening tests for type 2 diabetes

These have been recently extensively reviewed[32-35]. Some caution is required in interpreting the statistical results reported in these reviews and below because in many studies the diagnosis of diabetes was made using diagnostic criteria which predate the current WHO and American Diabetes Association (ADA) criteria. Despite this, the data allow conclusions about general performance of the various approaches to screening for type 2 diabetes.

5.2.4.1 Questionnaires

Several questionnaires have been developed to screen for undiagnosed diabetes and have included a range of questions covering both symptoms and recognised risk factors. If a person presents as a result of any of the symptoms of diabetes (such as thirst, polyuria etc.) and is confirmed to have the condition then this process is diagnosis and not screening. However, it is conceivable that people identified as having diabetes by means of a screening test or programme may, retrospectively, recognise the presence of symptoms which were not acted upon at the time. However, since the main purpose of screening is to detect asymptomatic people

with undiagnosed diabetes, questionnaires which are based on the symptoms of diabetes are not considered here.

The original ADA "Take the test: know the score" questionnaire[36] included both symptoms and historical risk factors. A modified version of this questionnaire has been evaluated by Herman et al[37] based on data from the Second National Health and Nutritional Examination Survey and had a sensitivity of 83%, specificity of 65% and PPV of 11%. This questionnaire was subsequently tested in a community screening program in Onondaga County New York and showed a sensitivity of 80%, specificity of 35% and a PPV of 12% [38,39].

Griffin et al developed a risk score based on risk factors routinely collected in clinical practice[40] and evaluated this in a hypothetical notional population with the same age-sex structure as England and Wales. No cut off for the risk score was prescribed but rather criteria for deciding a suitable cut point were proposed. An example gave a sensitivity of 77%, specificity of 72% and PPV of 11%.

5.2.4.2 Urine glucose

The usefulness of urinary glucose as a screening test for undiagnosed diabetes is limited because of the low sensitivity which ranged from 21% to 64% with specificity > 98% in studies which included performing an OGTT in the entire study population or a random sample of negative screenees[32].

Examples of such studies include Davies et al[41] who used a self-test for postprandial glycosuria and reported a sensitivity of a positive urine test of 43% and specificity 98%. Hanson et al[42] studied Pima Indians with non-fasting urine glucose and non-fasting OGTT and reported a sensitivity of 64% and specificity of 99% for a positive urine test for diabetes diagnosed on the 2-hour non-fasting post glucose load plasma glucose result.

Friderichsen and Maunsbach[43] screened 2,242 people with a self-test for postprandial glycosuria and tested all people with a positive result and a random sample of 106 negative screenees with an OGTT and reported a sensitivity of 21% and specificity of 99%.

Despite its low sensitivity, urine glucose testing may have a place in low resource settings where no other procedure is possible. This is particularly so, of course, when the prevalence of undiagnosed diabetes is likely to be high.

5.2.4.3 Blood glucose

Many studies of this question have used the blood glucose measurement which was part of the diagnostic test. In addition many studies have included people with diagnosed diabetes in the statistical analysis of test performance. Only studies which excluded people with diagnosed diabetes are considered below.

Venous fasting plasma glucose[32] has a sensitivity between 40% and 65% with a specificity > 90% for FPG values ranging from 6.1 – 7.8 mmol l^{-1}. Since the introduction of the new WHO and ADA diagnostic criteria for diabetes attention has focussed on comparisons of the cutoff point between normal and abnormal - FPG of 6.1 mmol l^{-1} as recommended by ADA and 5.5mmol l^{-1}, being the WHO cut point below which the diagnosis of diabetes is unlikely. Although a number of studies have supported the lower FPG value, there is no universal agreement on this point and ultimately the choice of cutpoint must be determined by the purpose of the screening programme and the resources required and available to perform further testing on the proportion of the population which would be identified by the choice of cutpoint[33].

Examples of studies which reported optimal sensitivity and specificity at the lower cut-point include Costa et al[44] who reported that this was achieved at an FPG ≥ 5.4 mmol l^{-1}, Larsson et al[45] at an FPG of 5.3 mmol l^{-1} and Cockram et al[46] at an FPG of 5.6 mmol l^{-1}. Modan and Harris[47] compared various FPG levels in people in the USA and Israel and concluded that no FPG level provided a satisfactory cutoff point to use in screening for undiagnosed diabetes. However an FPG of ≥ 5.55 mmol l^{-1} performed better than other levels with a sensitivity of 83% and 95% respectively in the USA and Israel with corresponding specificities of 76% and 47%, and PPVs of 17.2% and 11.8%.

A number of studies in different populations have reported on the performance of an FPG of 6.1mmol l^{-1}.

They report sensitivities ranging from 58%-87% (median – 81%) and specificities ranging from 75%-98% (median 92%)[33].

Fasting capillary blood glucose has also been used for screening. Bortheiry et al[48] reported that the best equilibrium between sensitivity and specificity for the diagnosis of diabetes was achieved at a cutoff of 5.6 mmol l^{-1} for fasting capillary blood glucose in their study of 4,019 Brazilian people undergoing an OGTT.

Studies on the usefulness of **random blood glucose** (RBG) as a screening test have mostly used random capillary blood glucose (RCBG) measured with a blood glucose meter. Two interrelated issues arise (1) the usefulness of RBG/RCBG in screening and (2) the accuracy of blood glucose meters for use in screening programmes.

There are few well designed studies which have properly addressed these issues with the main methodological problem being the failure to determine the overall prevalence of undiagnosed Type 2 diabetes in the cohort being studied by performing an OGTT in everyone or in a sample.

Three studies have examined RCBG (measured by reflectance meter) as a screening test for diabetes and performed an OGTT in the whole population irrespective of the RCBG result. Qiao et al[49] reported a sensitivity of 79% in men but only 40% in women while specificity was 86% and 84% respectively for men and women using for a value of 5.8 mmol l^{-1}. Engelgau et al[50] reported that a value of 5.6 mmol l^{-1} achieved a sensitivity ranging from 68%-74% and specificity ranging from 66%-77% depending on age. The authors concluded that different cutpoints are required to account for the postprandial period and age. Rolka et al[51] reported that RCBGs of $\geq$ 7.8mmol l^{-1} and $\geq$ 6.7mmol l^{-1} had sensitivities of 75% and 56% and specificities of 88% and 96% respectively.

The other important consideration with blood glucose meter measured readings is the accuracy of the result. While these are sufficiently accurate for day to day monitoring of diabetes control, their accuracy in screening for undiagnosed diabetes in routine practice, as opposed to the carefully controlled situations which have applied in published studies, has been questioned and attention drawn to the potential inherent inaccuracy

of the method[52]. However these problems are not necessarily insurmountable and the final decision about their use will depend on resources and related practical considerations.

5.2.4.4 Glycated haemoglobin

The desire to replace the OGTT with a simpler test has been a major factor behind the evaluation of glycated haemoglobin as a screening test for undiagnosed type 2 diabetes. Peters et al[53] performed a systematic review of articles published between 1966 and 1994 in which glycated haemoglobin (HbA_{1c}) was measured concurrently with performing an OGTT. When an HbA_{1c} plus 4SDs was used as a cutoff point, the sensitivity was 36% and specificity 100% compared with OGTT diagnosed diabetes using 1985 WHO criteria. An HbA_{1c} cutoff point of 6.1%, which had been found to correspond most closely with a 2-hour plasma glucose concentration of 11.1 $mmol^{-1}$ in Pima Indians, included 41% of non-diabetic subjects and 21% of subjects with IGT [53].

Davidson et al[54] examined HbA_{1c} levels from the NHANES III study and from the Meta-Analysis Research Group cohorts[52]. Using the 1997 ADA criteria for diagnosing diabetes, 60% of people in both datasets having diabetes diagnosed on the basis of an FPG of 7.0-7.7 $mmol\ l^{1}$ had normal HbA_{1c} and one third had results within 1% of the upper limit of normal.

Measurement of HbA_{1c} is not yet standardised around the world and has significant biological variation in non-diabetic subjects[55]. There is currently insufficient evidence to enable a judgement to be made regard to its performance as a screening test.

Fructosamine has been used less frequently than glycated haemoglobin measurement, and has not performed well because of sensitivities as low as 19%[32].

5.2.4.5 Combinations of tests

Screening tests, as mentioned above, may be combined to improve performance. In relation to type 2 diabetes this can be done using the tests serially (e.g. assessing

risk by questionnaire followed by blood glucose measurement if a certain risk score is reached) or simultaneously (e.g. measurement of blood glucose and HbA_{1c} at the same time). Combination testing is more resource intensive, especially if applied sequentially.

Tests performed in parallel using FPG and HbA_{1c} or fructosamine have been reported to have a sensitivity ranging from 40% to 83% and specificity of 83%-99%, depending on the cut off values chosen[32]. Combining the modified ADA questionnaire and RCBG ≥ 6.7 mmol l^{-1} achieved a sensitivity of 58% and specificity of 94%[51].

An illustration of the effects of serial combination testing is shown in Table 4 for a screening protocol which initially assessed risk factors, performed FPG in those at risk, then measured HbA_{1c} in those with an FPG between 5.5 and 6.9 mmol l^{-1}, and then tested with an OGTT those who had an HbA_{1c} ≥ 5.3%. This example illustrates that serial testing results in decreasing sensitivity, increasing specificity and PPV and reduces the number of people requiring definitive testing.

Multivariate logistic regression modelling with derivation of a probability value is another approach to combining demographic, clinical and biochemical tests in screening for undiagnosed diabetes. Tabaei and Herman[56] combined age, sex, BMI, postprandial time and random capillary plasma glucose to calculate the probability of undiagnosed diabetes and therefore the need for an OGTT. The calculation can be performed on a hand held programmable calculator and had a sensitivity of 65%, specificity of 96% and PPV of 63%.

5.2.4.6 Public response to screening for type 2 diabetes

Not much is known about the public response to diabetes screening programmes. This is important in that the sensitivity of a screening programme, even if based on a test or tests of optimum sensitivity, will be severely reduced if uptake is low. Epidemiological studies of diabetes prevalence in the general population could serve as proxies to provide this information, but only prevalence studies with a high response rate are reported in the literature.

In the few available studies that do report the response to a diabetes screening programme, it is in the range of 30% - 80%[57-60]. In all these studies the population invited for screening was defined by a specific age range only. There are no reports on whether the response of these populations would have been different if a higher-risk population were invited, defined by several known risk factors (age, obesity, family history etc.).

5.2.4.7 Frequency of testing

There are no compelling data on which to decide the optimum frequency of screening for type 2 diabetes. One possible source of information could be studies of diabetes incidence or progression to diabetes from normal glucose tolerance, IGT or IFG.

The annual rate of progression from IGT and IFG to diabetes is 3% - 13% [61,62], which might argue for annual re-screening in people with IGT and/or IFG. However, there are fewer studies of the incidence of diabetes in normoglycaemic individuals. The available data indicate that the annual progression from normoglycaemia to diabetes is in the range of 0.6% - 1.2%, depending on the population and the age group studied.

On the basis of the available data, the ADA have recommended screening of middle-aged normoglycaemic individuals at 3-yearly intervals[63], while the British Diabetic Association (now Diabetes UK) recommended screening of 40-75 year-olds every 5 years if they have none of the recognised risk factors, and every 3 years in the presence of risk factors[64].

5.2.5 Assessing the risk of future development of type 2 diabetes

In addition to the detection of undiagnosed type 2 diabetes there is increasing interest in identifying people without diabetes who are at increased risk of the future development of the condition. Any screening strategy which aims to identify people with undiagnosed diabetes which includes an OGTT will identify some people with IGT and IFG and screening strategies which use an FPG will identify people with IFG.

Stern et al used a multiple logistic regression model to predict 7.5 year incidence of type 2 diabetes using readily available clinical information[65]. The model included age, sex, ethnicity (Mexican American/non Hispanic white), FPG, systolic blood pressure, HDL cholesterol, BMI and parent/sibling with diabetes. This model performed similarly well by area under the ROC curve with and without inclusion of the 2h OGTT blood glucose value.

The Finnish Risk Score is a recent example of a risk assessment tool designed to identify people at risk of the future development of diabetes without the need for laboratory tests[66]. The risk score included age, BMI, waist circumference, history of antihypertensive drug use or high blood glucose, physical activity and daily consumption of fruit and vegetables. A score of ≥ 9 had a sensitivity of 77% and specificity of 66% and PPV of 7% in a large cohort followed for 10 years.

6 The current evidence base

6.1 Evidence relating to the efficacy of early detection

There are currently no definitive RCT data available on the efficacy of early detection of diabetes through screening. A number of relevant studies are in progress or have recently reported, albeit with weaker designs than RCTs.

'INTER-99' is a study currently taking place in Copenhagen county, Denmark. In this study, over 13,000 residents aged 30-59 were invited to take part in a screening programme and were randomised to intervention (90%) and control (10%) arms. Just over 50% (6,784) accepted the invitation and were tested with a standard 75 g OGTT. In the intervention group, people with newly diagnosed diabetes, IGT or at high risk of CVD (the upper quintile of risk) were invited to participate in a lifestyle modification programme concentrating on reducing fat and energy consumption and increasing physical activity. In addition, people received 'usual care' with respect to medication through their local practitioners. In the control group no specific action was taken and these people receive only usual care. The results are likely to be available in 2006.

The (Anglo-Danish-Dutch) ADDITION study[67] is screening over 200,000 individuals aged 40-69 years for diabetes in a step-wise screening strategy. It first identifies high risk individuals by means of a risk score and then confirms or otherwise a diagnosis of diabetes based on glucose concentrations at fasting and/or 2h after a 75g glucose load. As a result of this process, a predicted 3,000 individuals will be randomised to standard treatment or target-driven intensive pharmacological and non-pharmacological treatment. The specified end-points are all-cause mortality and fatal or non-fatal macrovascular events. The study evaluates the effectiveness of screening and

intensive treatment with regard to these primary endpoints, the secondary endpoints of microvascular complications, the cost-effectiveness of this approach and psychosocial factors such as stress and anxiety related to screening and subsequent treatment.

The study by Schneider et al[68] carried out in the former German Democratic Republic provides an analysis of a mass-screening programme based on urinary glucose levels, conducted in the former East Germany in the 1960's and 1970's. It suggested that those found, by screening, to have diabetes had an improved outcome compared with those presenting spontaneously with diabetes. However, the methods used in this study would not be acceptable given current criteria for RCTs.

In a *post-hoc* analysis of UKPDS (UK Prospective Diabetes Study) data the frequency of subsequent complications in relation to FPG on entry to the trial has been carried out[69]. The rationale behind this analysis is that FPG concentration on entry might serve as a surrogate for the duration of diabetes prior to recruitment. No significant difference in the frequency of end-points between 'incidental' and 'non-incidental' cases with FPG 10 mmol l^{-1} and above was seen. However, a significantly lower rate of all major end-points was seen in the group with initial FPG <7.8 mmol l^{-1} compared with the =>10 mmol l^{-1} group and significantly lower diabetes related death rates and myocardial infarction rates when the <7.8 mmol l^{-1} group was compared with the <7.8 – 10 mmol l^{-1} group.

Although the UKPDS was not intended to test any *a priori* hypothesis related to the early detection of diabetes, these findings do suggest a benefit of intervention either at lower levels of FPG or at earlier stages of the natural history of diabetes and this may be consistent with a benefit derived from early detection. This latter inference is crucially dependent on whether or not the value of FPG is an indicator of prior duration of disease or simply a marker of the severity of the disease.

One of the purposes of screening for diabetes may be to reduce the risk of cardiovascular disease in people with hyperglycaemia.

People with IGT and diabetes are at greatly increased risk of cardiovascular disease, including heart disease, stroke and peripheral vascular disease[70]. This risk appears to be associated with both hyperglycaemia[71] and to an increased frequency of other recognised cardiovascular risk factors in people with diabetes[72]. Cardiovascular risk does vary according to the diagnostic criteria used, with glucose tolerance apparently more strongly associated with risk than fasting glucose levels[73]. Glycated haemoglobin levels also predict cardiovascular risk in non-diabetic as well as diabetic individuals[74].

There is also now evidence that drugs that reduce cardiovascular risk are highly effective in people with diabetes (for example antihypertensives[75], statins[76]).

Diabetes screening may therefore be considered as one element of a wider programme to identify individuals at increased cardiovascular risk who could benefit from pharmacological treatments and lifestyle change to reduce their cardiovascular risk. In practice this integration often already occurs where cardiovascular disease is a significant public health issue and policy for primary or secondary prevention of cardiovascular disease has been developed. For example, WHO guidelines recommend screening for diabetes in individuals with hypertension[77] and the National Service Framework for Coronary Heart Disease in the United Kingdom recommends screening for diabetes in individuals with documented cardiovascular disease[78].

The appropriate relationship between cardiovascular risk reduction programmes and screening for diabetes will depend on local circumstances. If there is already a cardiovascular risk reduction programme, then the most cost-effective way of introducing screening for diabetes is likely to be an integrated programme that identifies individuals at high risk of both diabetes and cardiovascular disease and offers appropriate pharmacological and lifestyle interventions for both. This may influence the choice of population screened (targeting older individuals with other cardiovascular risk factors such as hypertension, for example). It may also influence the choice of screening test (if a fasting sample is taken it could be tested for both lipids and glucose).

In populations where cardiovascular disease is not a major cause of morbidity and screening is more appropriately directed at reducing microvascular complications, screening may target younger individuals who are at lower cardiovascular risk but do have a high lifetime risk of microvascular complications. Similarly the choice of a glucose tolerance test or fasting glucose measure to identify diabetes may partly depend on whether the focus is on reducing cardiovascular or microvascular risk.

6.2 Evidence relating to economic aspects of early detection

Descriptive data on costs suggest that the health care costs of the screening itself are relatively low though there may be a substantial, and as yet unquantified, opportunity cost both to the system and to the individuals concerned. The costs of the subsequent treatment of diabetes are likely to be much higher than the screening costs. As the effectiveness of the management of diabetes becomes greater, the relative benefits of early detection will become less.

Without direct evidence of the effectiveness of early intervention, there can be no definitive statement of its cost-effectiveness. However,

modelling studies have been undertaken. For example, in the USA, the CDC Diabetes Cost Effectiveness Study Group published the results of an economic appraisal comparing the life time cost and benefit of opportunistic screening for type 2 diabetes in adults with the then current clinical practice[79]. This group considered only direct medical costs from a single payer's perspective. The benefit was analysed by using a computer simulated model incorporating the benefit of preventing and reducing long term micro vascular complications. The results demonstrated that opportunistic screening increases the lifetime costs of treatment by $3,388 but results in a gain in life-years of only 0.02 years (1 week). To gain an additional life-year, the incremental cost of screening over current clinical practice was estimated at $236,449, and the cost per QALY gained was estimated at $56,649.

These same authors also compared the cost-benefit ratio of opportunistic screening for diabetes with that of breast screening for women aged 50 and above costing $34,000-$83,830 per life year gained, cervical screening for women above 21 years of age costing $50,000 per life year gained and hypertension screening for adult men and women costing $48,000 and $87,000 per life year gained respectively. Screening for type 2 diabetes thus compares unfavourably with these other options.

In Taiwan, Chen et al[80] used a computer simulation model to estimate the cost per QALY and life years gained comparing two mass screening programmes at two and five year intervals. The costs compared included cost of screening and clinical care of diabetes and its long term complications. The population disease progression model used in the computer was derived from studies in the local Taiwan population with, at that time, a prevalence of diabetes of 6%-12%. Unlike the CDC simulation mentioned above, the authors included the possible effect of reduction in macro vascular complications in their model.

This Taiwan simulation estimated a much lower cost of mass screening programme per life year gained compared to the opportunistic screening costs estimated by the CDC group. In Taiwan, the incremental costs for biennial screening regime were estimated at $26,750 per life-year gained, and $17,833 per QALY. The corresponding figures for five-yearly screening regime were $10,531 per life-year gained and $17,113 per QALY. Although this comparison is interesting, it would be misleading to draw firm conclusions from it since the assumptions made were not identical in the two studies and they relate to different populations. One particular difference between the models is whether the benefit of reducing macrovascular complications is or is not included.

In the absence of direct evidence on the effectiveness and cost-effectiveness of screening for type 2 diabetes, simulations such as these

which are totally explicit in the assumptions made, can prove useful guides as to the utility of screening in any given population.

6.3 Evidence relating to the psycho-social effects of early detection

This is an under-researched area in general and in particular in relation to type 2 diabetes. Johnson et al[81] report on levels of anxiety in relation to screening for type 1 diabetes. Parents of ICA positive children were reported to have the highest levels of anxiety followed by spouses of positive individuals with at risk children having the lowest levels of all.

Studies of conditions related to diabetes – hypertension and CVD are also available. A systematic review of the psychological impact of predicting individual risk of illness[82] included 21 studies related to CVD as well as two related to type 1 diabetes. Overall, the results showed a range from increased anxiety, depression or psychological distress through no effect to decreased levels. People undergoing multi-channel chemistry screening[83] generally show a short term increase in anxiety which dissipates over time. Abnormal results are associated with significant decrease in levels of perceived physical health, general health, perceived health and pain. The people most affected are those not offered any support.

More recently, Griffin *et al*[84] have suggested that screening for diabetes does not cause adverse psychological effects provided appropriate explanations of the procedure are given and provided there is appropriate follow-up. These conclusions have been strengthened by recent studies from The Netherlands[85] and from the USA[86]. The former interviewed 40 subjects involved in the Hoorn 'stepwise' population project which screened for diabetes. Twenty of these people had been found to have previously undiagnosed diabetes and 20 were at increased risk of having diabetes but did not, at least at that time, meet the diagnostic criteria for the condition. Although (or perhaps because) the newly diagnosed subjects had little understanding of the relevance of their diagnosis, only one was alarmed by it. Both groups expressed positive views about the screening. In the US study[86], screening for type 2 diabetes at the Durham Veterans Affairs Medical Center identified 56 people with previously unknown diabetes (out of 1,253 45-64 year olds screened) who had similar SF-36 Physical Component Scores and Mental Component Scores to those who did not have diabetes, both at the time of screening and after one year.

Clearly these findings need to be confirmed with other subjects in other cultures. As public awareness grows of the significance of a diagnosis of diabetes and its possible long term consequences, the psychological effects may be more marked.

7 Formulating policies about screening for type 2 diabetes

Figure 1 summarises the issues which need to be taken into account when formulating a screening policy. Three epidemiological considerations have been included, four of health system capacity and two economic considerations. Each of these should be viewed as a spectrum from, at one end, a clear indication that screening should be instituted to, at the other, clear evidence that it should not. Any population at any one time will be at a given point along each of these spectra. The policy decision as to whether or not to institute screening will be a judgment which cannot, necessarily, be extrapolated to other situations.

In reaching this judgement, public health authorities, clinicians, diabetes associations and others should consider the following:

7.1 The aims and objectives of a screening policy

Aims should be clear and relevant to the context of screening individuals at risk of having undiagnosed diabetes or at risk of developing diabetes. These may relate to be the immediate effects of diabetes (e.g. infections), to the prevention of microvascular complications, to the prevention of CVD or to a combination of these. Thus, of crucial importance in relation to framing aims and objectives is knowledge about the most important consequences of diabetes in the population being considered.

7.2 Epidemiological considerations

The most important epidemiological consideration is the prevalence of undiagnosed type 2 diabetes; this is known for some countries and regions as a result of field surveys of diabetes using OGTT; where it is unknown, estimates can be made by extrapolation (ratio of previously undiagnosed to known diabetes is likely to be around 1:1 or 2:1 (Table 2) but might be as extreme as 1:2 (e.g. Brazil) or 6:1 (Tonga). If unknown, this can be determined by a relatively simple survey. If screening of any kind is initiated, data on the numbers of unknown cases identified need to be collected and analysed periodically.

7.3 Considerations of health system capacity

The main issues here are – the capacity of the system to carry out screening, follow-up and diagnostic testing and its capacity to manage effectively the newly detected cases of diabetes. The system must also be able to support individuals when the results of the screening are known, whether true positives, false positives or false negatives. The identification of people with IGT and IFG is a by-product of screening for type 2 diabetes and any screening policy needs to specify a clear

care pathway for such people Other issues are the capacity of the system to assess individual risks by using routinely available data. The first 'screen' might be made from such data[87] thus eliminating one attendance by the individual.

7.4 Economic considerations

The cost of a screening programme will vary depending on the costs of materials, personnel etc. in any given setting. A large determinant of cost is whether the activity is conducted as a de novo activity or builds on existing health (e.g. primary care) infrastructure. Clearly, the former is more costly. Also varying costs in getting the person to the test. Cost of subsequent care will also vary widely (e.g. $10,000/yr in USA vs. $100/yr in India. It is the second of these (cost of subsequent care) which is the larger component of cost. May be difficult to build a holistic economic argument since direct costs and indirect costs fall on different public or private sectors and the funding of screening and subsequent treatment may come from different budgets lines.

Costs of screening may be reduced if screening uses routinely available information (for example using routine clinical information systems to identify people at high risk of diabetes) or by linking to other screening programmes (for example screening for glucose and lipids on the same fasting blood sample as part of a cardiovascular screening programme). Cost-effectiveness of treating screened individuals may also be increased by screening populations at particularly high risk of preventable adverse outcomes, for example populations with a high risk of cardiovascular disease. However, even the screening of high risk populations, such as those already known to have hypertension and dyslipidaemia[88], can be costly. O'Connor et al[88] identified 1,548 such patients being cared for by a large medical group in Minnesota. After exclusion of those who had already been screened in the past year, those already known to have diabetes, those lost to follow-up (died or left the scheme etc.), one newly diagnosed case was discovered for every 40 high risk patients screened. This low yield resulted in a cost of US$ 4,064 per case identified.

7.5 The choice of a test or tests

This is a judgement dependent upon the characteristics of a test (sensitivity, specificity etc.) the cost of a test in any given context and the capacity of the system to apply the test. Costs are largely driven by the rate of detection of positives (true and false) and the need to follow these up and carry out diagnostic testing.

7.6 Competing priorities

There will be competing priorities within diabetes – increased care for people with known diabetes v identifying new cases; also in the wider health care context - other health priorities such as communicable diseases; these need to be reassessed on an ongoing basis.

7.7 Ethical and political considerations

Valid argument for considering it the right of any individual to have diabetes diagnosed; this right needs to be weighed against any harm, anxiety etc. that may occur as a result of earlier diagnosis; also the harm done to false positive and false negative individuals; there is an opportunity cost if screening is carried out because the resources devoted to screening cannot be used for other purposes. No screening programme can be instituted without a political will to do so. The political will to institute screening may run counter to the supporting evidence.

Different expectations and ethical imperative depending on how the person comes to the test: disease – patient comes to seek advice screening – health professional imposes something on patient also medico-legal ramifications of not screening.

8 Widening the evidence base

8.1 The need for evidence from randomized controlled trials

The benefits of early detection of type 2 diabetes through screening are not clearly established. The few available studies suffer from several types of bias that may lead to spurious conclusions regarding the benefits of screening .

The main sources of bias are as follows:

Lead-time: the interval between the time of detection by screening and the time diabetes would have been diagnosed in the absence of screening. Thus lead-time bias prolongs the apparent duration of survival and/or complication-free period simply by advancing the diagnosis.

Selection bias: People who enter screening programmes are volunteers who are almost always more health conscious than the rest of the population. Thus they are more likely to have a better disease outcome even without screening.

Length-time bias: This relates to the fact that individuals with rapid metabolic deterioration will tend to develop symptoms that prompt

them to contact health services. Thus only people with slowly progressing and milder disease remain to be identified by screening. These people are likely to have a better clinical outcome than rapidly progressing cases, regardless of the treatment.

Over-diagnosis bias occurs when enthusiastic screening results in diagnosing diabetes in people that do not have it. Since non-diabetic individuals have a more favourable life course than persons with diabetes, this difference in the outcome may be erroneously attributed to screening.

Randomized controlled trials (RCTs) are usually regarded as the best means to evaluate the effectiveness of screening and early treatment. They are superior to observational studies because, if randomisation is successful, the possible confounding effects of individual attributes and health-related behaviours other than the decision to take up screening can be eliminated[89].

One of the reasons why data from RCTs that apply available treatment to a screened group, but not a control group are unavailable, is that such studies require long-term follow-up of a large number of participants. The feasibility of RCTs is further decreased by the need to account for people who refuse to participate, as well as for people in the control group who are offered and accept screening outside the programme. Nevertheless, RCTs which can take into account these issues are potentially feasible and should be encouraged.

8.2. The need for observational studies

RCTs to evaluate screening for diabetes have not been conducted so far, and even observational studies are scarce, in contrast to screening several other chronic conditions, particularly some of the cancers.

Once a screening method has been shown to be effective in an RCT, cohort studies in the general population could measure how a particular screening programme performs in a specific population. A cohort study could demonstrate the rate of particular outcomes among participants, refusers and non-invited subjects or screened versus non-screened communities.

In contrast to RCTs and cohort studies, case-control studies estimate the individual's risk reduction if screened, although the protective effect of the screening procedure itself is not quantifiable. Although case-control studies are often regarded with scepticism on account of length-time, lead-time and selection biases, these can largely be accounted for with appropriate design and analysis[90]. Case-control studies cannot replace RCTs for the evaluation of the effect of screening, but they can be used to monitor a programme's effectiveness once screening has been widely introduced[91].

Recently, the STARD initiative[92,93] has made recommendations for the reporting of studies of diagnostic accuracy. These recommendations include a checklist and flow diagram for the elements (such as the numbers of eligible patients, exclusions, abnormal, normal and inconclusive results etc.) vital to the interpretation of results. By analogy, standardisation of the reporting of observational studies of screening would facilitate their interpretation and enable their generalisability to be more easily assessed.

As a result of discussions at the WHO/IDF meeting, it was decided to establish the 'DETECT-2' collaboration. This will compare and evaluate selected strategies for screening for undiagnosed type 2 diabetes across a range of populations from diverse ethnic backgrounds and to establish simple screening strategy options. DETECT-2, by using population based data from various populations will examine the prognostic implications with regard to morbidity and mortality for individuals categorised on the basis of a screening programme for type 2 diabetes.

8.3. The need for economic evidence

There are only two cost-utility evaluations for type 2 diabetes, one comparing opportunistic screening and the other comparing mass screening with routine care[94,95]. The US study did not include the benefit of preventing macrovascular complications. The study in Taiwan demonstrated that screening may be cost-effective in countries with high diabetes prevalence. There are no studies that have looked at cost-utility of screening for diabetes in populations deemed to be at high risk of type 2 diabetes.

8.4. The use of modelling studies

All issues around the effectiveness of screening for diabetes cannot realistically be resolved by RCTs. The development of less costly and less time-consuming methods is to be advocated. One study used a Markov model to evaluate the efficacy of population screening for diabetes[96], and another used the Monte Carlo model to estimate the lifetime costs and benefits of opportunistic screening for diabetes (CDC 1998). Both indicated there could be economic grounds for screening. Although modelling studies do not provide answers, they direct attention to the right questions which can then be addressed in empirical studies.

8.5 The need for evidence on the psycho-social effects of early detection

Screening may lead to over-diagnosis, inappropriate investigation and treatment, avoidable adverse effects and unnecessary psychosocial and economic costs[97]. However, there are no studies specifically examining

these issues in diabetes. Physical harm associated with screening for diabetes may be considered negligible, but psychological and social harm could be more substantial.

A diagnosis of Type 2 diabetes has potential implications for employment and personal insurance. Treatment with insulin precludes some forms of employment and insurance premiums are higher for persons with diabetes. Anxiety caused by false positive results in screening for diabetes is unlikely to be as high as that caused by false positive results in screening for cancer. However, since screening programmes involve a large number of people, even a small adverse effect on quality of life or health-related behaviour could affect public health. Therefore, studies of the psychosocial effects of screening in diabetes are needed to complement studies of effectiveness.

9 Implementing policies about screening for type 2 diabetes

Two examples of national policies, from Brazil and Mexico, favouring screening for type 2 diabetes are given on the following pages. While not necessarily advocating these approaches, the examples are provided here as illustrations of programmes which have been implemented on a large scale.

The Case of Brazil

Brazil recently performed nationwide community screening for diabetes and hypertension as part of its National Re-organization Plan for the Care of Diabetes and Hypertension. In addition to detection of undiagnosed diabetes, the purpose of the screening programme was two-fold:

- to raise public awareness of the importance of diabetes and hypertension, and
- to focus the efforts of primary care and health administrators on the restructuring and capacity building necessary for adequate diagnosis, basic treatment, and prevention of complications of diabetes within the primary care sector as well as for the creation of adequate referral networks.

Following an initial countrywide training of over 13,000 health professionals in the diagnosis and treatment of diabetes, a mass media campaign invited members of the public to participate in capillary glucose testing in March and April of 2001. Over 5300 municipalities participated in the effort.

During the campaign, 21.8 million (73% of those targetted, adults $\geq$ 40 years of age) were tested with glucose meters. Of these, 1% (about 0.25 million) had values $\geq$ 15mmol/l (270mg/dl) and were referred directly for medical management. An additional 3% (about 0.61 million) had glucose screening values above the diabetes cut-off points, and immediately received a referral for confirmatory diagnostic testing.

An additional 12% (3.4 million) were test positive at lower values (fasting $\geq$ 5.5mmol/l (100mg/dl) or non-fasting $\geq$ 7.8mmol/L (140mg/dl) and were counselled to return within 3 months for further evaluation. Within 6 months of the screening programme, an additional 1.2 million fasting glucose determinations were performed by outpatient laboratories of the National Health System, presumably, in great part, as a result of the diagnostic demand induced by the program.

Evaluation of the process and costs of this programme are currently contributing to Brazil's effort to shift diabetes prevention and management out of hospitals and into primary care.

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The Case of Mexico: "You Have Diabetes but You Don't Know it"

In Mexico the 2000 National Health Survey demonstrated a prevalence of diabetes of 10.9% among those aged 20 years and over. This meant that in 2000 an estimated 5 million people were suffering diabetes in Mexico.

The Mexican Ministry of Health is conducting continuous diabetes (and hypertension) screening among those aged 20 years and over contacting their medical services for any reason. Volunteers are also evaluated during fairs and diabetes prevention activities such as those commemorating World Diabetes Day in some states. The target population of the government health care plan includes 41% of the Mexican population (about 41 million people in 2001).

The aim of the screening system is to identify those with undiagnosed diabetes to provide early treatment and prevent or delay the onset of long-term complications. It also focuses on the identification of those at high risk of presenting diabetes, aiming to decrease the frequency of known risk factors such as obesity, lack of physical activity and deficient diet. The screening process is divided in two phases. The first one is the identification of individuals at high risk of diabetes through the application of a questionnaire named "You have diabetes but you don't know it". This questionnaire has seven questions and includes the calculation of BMI and the measurement of the waist circumference. The questionnaire was validated previously for the Mexican population. During the second phase, those obtaining scores of 10 or more points in the questionnaire are tested for blood glucose. In cases with capillary fasting blood glucose of 100 mg dl or capillary non-fasting blood glucose of 140 mg dl, a confirmatory test is required. Confirmation of the diabetes diagnosis includes an Oral Glucose Tolerance Test (OGTT) if needed.

Those with newly diagnosed diabetes and also those at risk are referred to different services included in the health system to commence diabetes education and treatment (if indicated). They are also invited to participate in a social group of people called "Mutual-help Group". Those who obtained scores lower than 10 points in the questionnaire receive counselling about maintaining adequate weight, diet and physical activity. The first evaluation of this plan in 2000 included a pilot of 6,186 persons in four states, 43% were considered at high risk of presenting diabetes and 1.6% was diagnosed with diabetes.

The cost of the screening was estimated at US$8.36 per newly diagnosed person with diabetes. In 2001 overall 3,945,885 people were evaluated with the application of the questionnaire, 572,153 people were tested for blood glucose and a total of 273,149 people from 32 states were identified as newly diagnosed with diabetes. Results for 2002 showed that a total of 3,985,860 were evaluated through the application of the questionnaire, 576,825 blood glucose tests were conducted and 313,124 people were diagnosed with diabetes.

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10 Conclusions and recommendations

10.1 Conclusions

1 The issue of screening for type 2 diabetes is important both in terms of individual health, day-to-day clinical practice and public health policy.

2 There is currently no direct evidence* as to whether individuals will or will not benefit from the early detection of type 2 diabetes through screening.

3 Despite this lack of direct evidence, early detection through screening is already taking place both by inviting individuals from the general population to come forward for screening and, opportunistically, when individuals perceived to be at high risk of developing diabetes attend for health care (usually primary health care) for other reasons.

4 These activities present opportunities for collecting observational data which, although no substitute for direct RCT evidence, can provide important, circumstantial evidence about efficiency, costs and impact.

5 There is direct evidence that the incidence of diabetes can be reduced in people at high risk of the future development of type 2 diabetes who may be identified as a result of activities directed towards diabetes detection.

6 If screening can be shown to be beneficial, the most important *epidemiological considerations* determining whether to screen in any given population will be (1) the prevalence of undiagnosed type 2 diabetes in that population and (2) the degree to which type 2 diabetes is associated with risk of cardiovascular disease, diabetes specific complications and other important health outcomes in that population.

7 The most important *health systems considerations* will be its capacity (1) to carry out the screening (2) to provide effective health care for those who screen positive (3) to address the psycho-social needs of those who undergo screening and (4) to implement effective prevention in those who, though not confirmed to have diabetes at the time, are at high risk of its future development.

8 The most important *population considerations* will be (1) the acceptability of the screening programme to those invited to

* ***'Direct evidence' is that from randomised controlled trials (RCTs) specifically designed to answer questions related to early detection through screening.***

attend (2) the extent to which any lack of acceptability reduces uptake (3) the psychosocial impact of each screening outcome – positive and negative, 'true' and 'false' and (4) the ability of those found to be at risk of future development of diabetes to modify these risk.

9 The most important *economic considerations* are (1) the cost of early detection to the health system and to the individual (2) the extra costs of treatment following early detection and (3) the relative cost effectiveness of early detection compared with that of improving the care of clinically detected (as opposed to screen detected) cases.

10 The most appropriate protocol for screening for undiagnosed type 2 diabetes in a particular setting should consider (1) the sensitivity and specificity of the screening methods available (2) the number of people who will need to be screened (3) the number of people who will need subsequent diagnostic testing (4) resource implications and (5) costs.

11 Screening for type 2 diabetes is a dynamic topic in which new evidence will become available and further considerations will arise over time.

10.2 Recommendations

1 Health authorities and professional organisations should formulate policies concerning screening for type 2 diabetes even if the policy is that screening is not currently to be advocated. In formulating that policy, the benefits and costs to the individual and their well-being are of paramount importance.

2 There is an urgent need for direct RCT evidence on the effects of early detection of type 2 diabetes through screening. Such evidence should include health outcomes related to diabetes, cardiovascular disease, psychosocial outcomes and economic considerations for individuals, health systems and the wider society. Although RCTs directed to answering these questions may be costly and logistically difficult, there is, in the current state of knowledge, no ethical reason why they should not be undertaken.

3 Since the results of such RCTs will not be available for some time (if ever), there is also an urgent need to develop a framework (or model) which would permit countries to evaluate the cost-effectiveness of earlier detection of diabetes compared to other preventive and therapeutic interventions.

4 Testing apparently unaffected individuals at increased risk of having diabetes when these individuals attend for health care for other reasons (sometimes called 'opportunistic screening') *may* be justified provided (1) the reasons for testing are adequately explained to the individual (2) the health system has the capacity for the clinical management of those who screen positive (3) methods with adequate sensitivity and specificity are available (4) the psycho-social needs of those who screen positive and those who screen negative can be met and (5) the health system can implement effective preventive strategies for those confirmed to be at high risk for the development of diabetes. There is no evidence to justify haphazard screening.

5 If such opportunistic screening is advocated then this should be carried out according to a policy which should (1) be clear and relevant in its aims and objectives (2) be based as far as possible on sound evidence (3) take into account the epidemiology of type 2 diabetes and related cardiovascular disease risk in the population and (4) be sensitive to competing local health priorities.

6 The choice of the method or methods for screening will depend on the resources available, the acceptability of the methods in the population being screened and the levels of sensitivity, specificity etc. that are required. Methods of screening which might be regarded as unacceptable in high resource settings (e.g. testing for urinary glucose) may be suitable in low resource settings.

7 Where screening is already taking place, formal evaluation should be integral to these activities. The results of such evaluations could contribute to the general assessment of the value of early detection and should be used in the modification or curtailment of the activities being evaluated.

8 Given the dynamic nature of this topic, policies for screening for type 2 diabetes must be reviewed from time to time as new evidence accumulates.

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Annex 2 Acknowledgements

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Table 1 – Biochemical criteria (venous plasma) for the diagnosis of diabetes, impaired glucose tolerance and impaired fasting glucose or impaired fasting glucose*

	Glucose concentration, mmol l^{-1} (mg dl^{-1}) (Venous plasma)
Diabetes mellitus:	
Fasting ***and/or***	=> 7.0 (=> 126)
2-h post glucose load	=> 11.1 (=> 200)
Impaired glucose tolerance (IGT)	
Fasting (if measured)	< 7.0 (< 126)
and 2-h post glucose load	=>7.8 (=>140) and < 11.1 (< 200)
Impaired fasting glycaemia or impaired fasting glucose (IFG)	
Fasting	=> 6.1 (=> 110) and <7.0 (<126)
and (if measured)	
2-h post glucose load	< 7.8 (< 140)

*adapted from "Definition,Diagnosis and Classification of Diabetes Mellitus and its Complications, WHO Geneva, and the "International Diabetes Federation IGT/IFG Consensus Statement"[1,2]. Venous plasma, venous whole blood and venous capillary values are given in the original reports.

Table 2. Recent studies of the prevalence of known and previously undiagnosed diabetes in selected populations

Study	Country	Prevalence of previously undiagnosed diabetes (%)	Prevalence of known diabetes (%)	Ratio of previously undiagnosed to known diabetes
Levitt et al, 1993[98]	South Africa	3.1	3.3	1:1
Mooy et al, 1995[99]	The Netherlands	4.8	3.6	1:1
Park et al, 1995[100]	South Korea	5.1	3.9	4:3
Elbagir et al, 1996[101]	Sudan	2.2	1.3	2:1
Oliveira et al, 1996[102]	Brazil	2.0	5.1	1:2
Mbanya et al, 1997[103]	Cameron	0.7	0.5	3:2
Ajlouni et al, 1998[104]	Jordan	4.5	8.9	1:2
Harris et al, 1998[105]	USA	2.7	5.1	1:2
Jimenez et al, 1998[106]	Paraguay	3.6	2.9	1:1
Castell et al, 1999[107]	Spain	3.6	6.7	1:2
Shera et al, 1999[108]	Pakistan	7.1	4.0	2:1
Tan et al, 1999[109]	Singapore	4.9	3.5	1:1
Sekikawa et al, 2000[110]	Japan	4.8	5.3	1:1
Ramachandran et al, 2001[111]	India	4.5	10.5	1:2
Amoah et al, 2002[112]	Ghana	4.4	1.9	2:1
Dunstan et al, 2002[113]	Australia	3.7	3.7	1:1
Satman et al, 2002[114]	Turkey	2.3	4.9	1:2
Suvd et al, 2002[115]	Mongolia	1.9	1.2	2:1
Colagiuri et al, 2002[116]	Tonga	13.0	2.1	6:1

Table 3 – recent randomised studies demonstrating effective interventions in people with IGT

Study (Country) and reference	Initial participants and level of randomisation	Interventions and length of follow-up	Main outcomes
Da Qing Study (China)[117]	577 men & women >25y. IGT (single OGTT, WHO 1985 criteria). Cluster randomised (by clinic).	Diet, physical activity, diet & physical activity and general advice (control). 6 y follow-up	Cumulative incidence of diabetes at 6 y: 44%, 41%, 46% and 68% (in 4 intervention groups respectively). After adjustment, reduction in diabetes incidence was 31%, 46% and 42% compared to control group.
Finnish Diabetes Prevention Study (Finland)[118]	522 men & women, 40-64 y. BMI >25 kgm^2. IGT based on means of two OGTTs (WHO 1985 criteria). Individual randomisation.	Diet and physical activity or general advice (control). Mean follow-up 3.2 y.	Reduction by 58% in risk of diabetes in intervention group: 11% vs. 23% at 4 y. Incidence inversely associated with degree of compliance with intervention.
Diabetes Prevention Programme[119]	3,234 men & women =>25 y, BMI =>22 (in Asians), =>24 in other groups. FPG 5.3 to 6.9 mmol l^{-1} and 2-h OGTT plasma glucose 7.8 to 11.0 mmol l^{-1}. Individual randomisation.	Placebo or metformin (850 mg twice daily) both with general lifestyle advice or intensive lifestyle intervention. Mean follow-up 2.8 y.	Compared to placebo: 58% reduction in incidence of diabetes with intensive lifestyle intervention, 31% with metformin. Incidence at 3 years: 29%, 14% and 22% respectively.
The STOP-NIDDM Trial (North America & Europe)[120]	1368 men & women aged 40 to 70 y, BMI 25 to 40, IGT (WHO 1985 criteria) plus FPG =>5.6 and <7.8 mmol l^{-1}. Individual randomisation.	Placebo or acarbose (100 mg 3 times daily). General advice on diet, weight loss and physical activity. Mean follow-up 3.3y.	Cumulative incidence of 32% in acarbose group vs. 41% in placebo group.
TRIPOD[121]	235 Hispanic women with previous gestational diabetes. Individual randomisation.	Placebo or troglitazone. Median follow-up 30 months.	Compared to placebo: 56% reduction in diabetes incidence. After an 8 month wash-out period, beneficial effects of the drug still observed.

Table 4. Performance of Serial Combination Screening for Undiagnosed Diabetes in the Australian AusDiab study populations[113]

	Risk assessment alone	***Plus FPG 5.5-6.9 mmol l^{-1}***	***Plus HbA_{1c} [3] 5.3%***
*Sen**sitivity (%)***	87	78	68
Specificity (%)	48	75	93
PPV + (%)	7	13	31
PPV – (%)	99	99	98
% population requiring OGTT	53	25	8

Figure 1. Receiver operator characteristic (ROC) curve

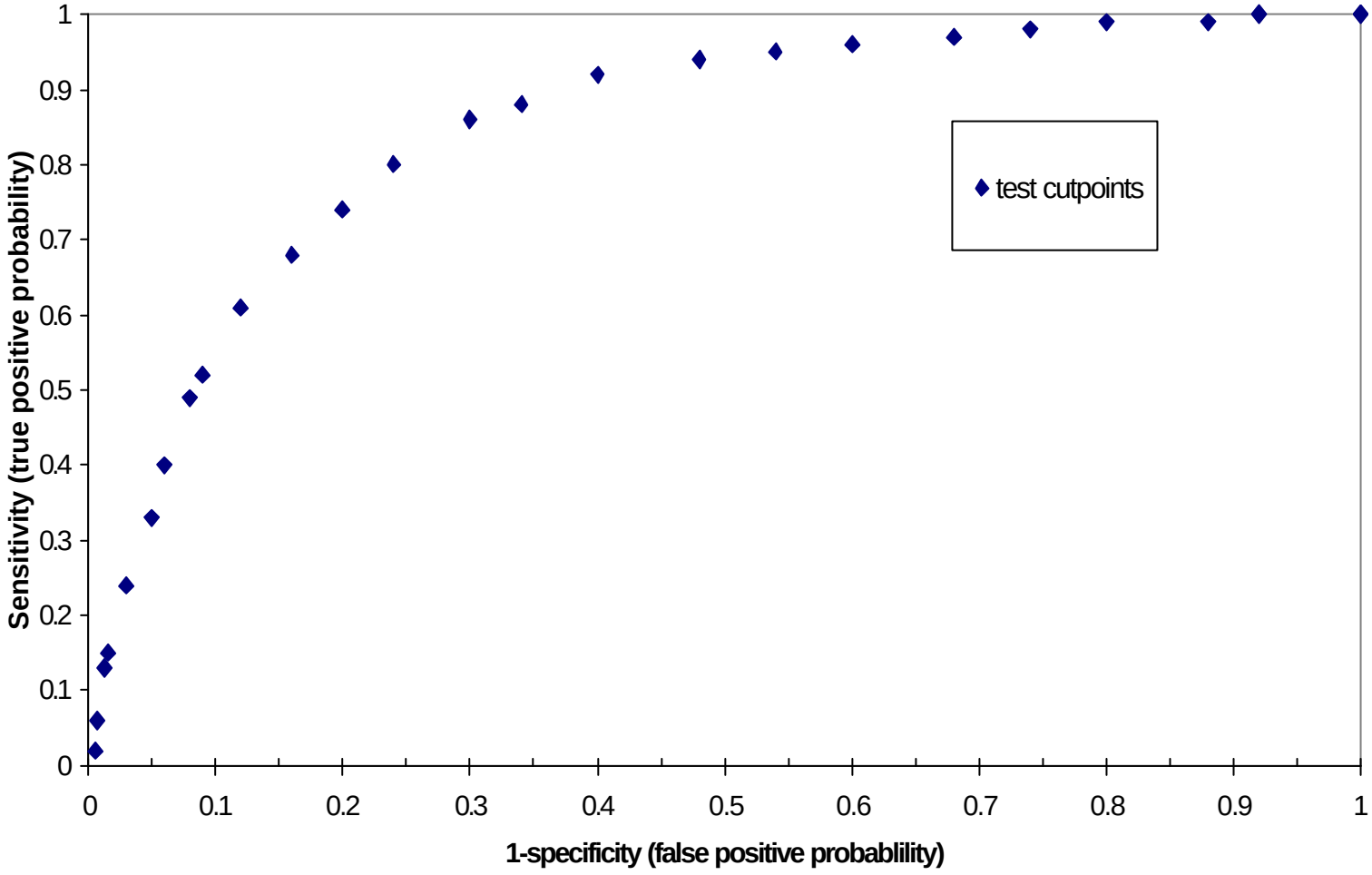
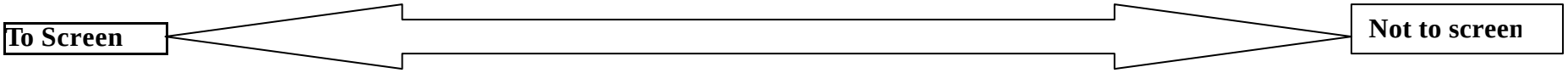


Figure 2 – considerations relevant to the development of a screening policy



Clear evidence that screening is beneficial	**Clear evidence that screening is harmful**
High prevalence of undiagnosed type 2 diabetes	**Low prevalence of undiagnosed type 2 diabetes**
High prevalence of cardiovascular disease (CVD) risk and other complications amongst people with type 2 diabetes	**Low prevalence amongst people with type 2 diabetes**
High capacity of health care system for screening	**Low capacity of health care system for screening**
High capacity of the health care system for effective clinical management of those who screen positive	**Low capacity of the health care system for effective clinical management of those who screen positive**
High capacity of the health care system for supporting the psycho-social effects of screening	**Low capacity of the health care system for supporting the psycho-social effects of screening**
High capacity of the health care system to implement prevention strategies in individuals at high risk of the future development of diabetes even those who screen negative on that occasion	**Low capacity of the health care system to implement these prevention strategies**
Low cost of early detection	**High cost of early detection**
Low cost of clinical management	**High cost of clinical management**

Epidemiological considerations | Considerations of health system capacity | Economic considerations

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