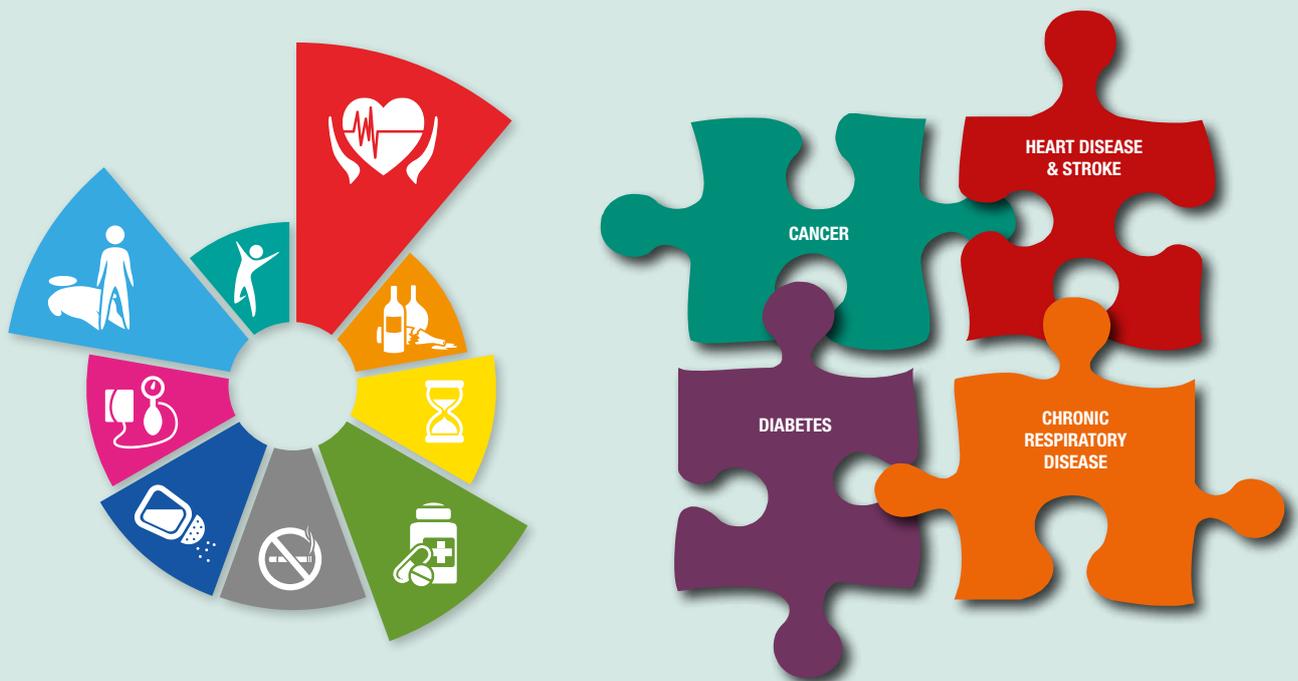# Implementation tools

Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings

World Health Organization

Implementation tools

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Introduction

Effective approaches to reduce the noncommunicable disease (NCD) burden in low-and middle-income countries (LMIC) include a mixture of population-wide and individual interventions. Such cost-effective interventions are already available and include methods for early detection of NCDs and their diagnoses using inexpensive technologies, non pharmacological and pharmacological approaches for modification of NCD risk factors and affordable medications for prevention and treatment of heart attacks and strokes, diabetes, cancer and asthma. These low technology interventions, if effectively delivered, can reap future savings in terms of reduced medical costs, improved quality of life and productivity. However, due to weak health systems, there are substantive gaps in their implementation particularly in LMIC.

Efficient use of limited health care resources, sustainable health financing mechanisms, access to basic diagnostics and essential medicines and organized medical information and referral systems are imperative for provision of equitable care for people with and at risk of NCDs. They require long-term care that is proactive, patient centered, community based and sustainable. Such care can be delivered equitably only through health systems based on primary health care (PHC).

Further, two billion people in the world are living below the poverty line and poverty and NCDs are linked through many pathways. Although providing good quality care for the poor is an ethical imperative, due to weak health systems and inadequate health-care expenditure of many countries, the poor do not have access to services at all or receive substandard services. Furthermore, out-of-pocket expenditure is unacceptably high in many LMIC. Countries need to transform and regulate health systems for universal access and social protection. This transformation will take several years given the global financial status and wide disparities in domestic resources between countries. In the meantime, Ministries of Health (MoHs) need to take steps to improve health outcomes and to reduce rising health-care costs due to NCDs and their preventable complications.

The WHO Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings is an innovative and action-oriented response to the above challenges. It is a prioritized set of cost-effective interventions that can be delivered to an acceptable quality of care, even in resource-poor settings. It will reinforce health system strengthening by contributing to the building blocks of the health system (table i, table ii). Cost effectiveness of the selected interventions will help to make limited resources go further

and the user-friendly nature of the tools that are been developed, will empower primary care physicians as well as allied health workers to contribute to NCD care (table iii). It should not be considered as yet another package of basic services but, rather, an important first step for integration of NCD into PHC and for reforms that need to cut across the established boundaries of the building blocks of national health systems. WHO PEN is the minimum standard for NCDs to strengthen national capacity to integrate and scale up care of heart disease, stroke, cardiovascular risk, diabetes, cancer, asthma and chronic obstructive pulmonary disease in primary health care in low-resource settings. Most importantly, it defines a minimum set of essential NCD interventions for any country that wishes to initiate a process of universal coverage reforms to ensure that health systems contribute to health equity, social justice, community solidarity and human rights.

Why do we need these implementation tools?

■ These tools of the WHO Package of Essential Noncommunicable Diseases Interventions (WHO PEN) support implementation of very cost effective interventions through an integrated approach.

■ Implementation of WHO PEN is a key component of the objective 4 of the Global Action Plan. These tools will enable early detection and management of cardiovascular diseases, diabetes, chronic respiratory diseases and cancer to prevent life threatening complications (e.g. heart attacks, stroke, kidney failure, amputations, blindness).

■ Effective implementation of WHO PEN, combined with other very cost effective population-wide interventions, will help even resource constrained settings to attain the global voluntary targets related to reduction of premature mortality and prevention of heart attacks and strokes*.

■ Equitable financing of interventions in WHO PEN can be a first step for addressing prevention and control of noncommunicable diseases within the universal health coverage agenda.

* A 25% relative reduction in risk of premature mortality from cardiovascular disease, cancer, diabetes or chronic respiratory disease

* Prevention of heart attacks and strokes by providing treatment (including glycemic control) and counselling at least to 50% of eligible people (those with a 10 year cardiovascular risk equal to or above 30%) and reducing their cardiovascular risk.

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Table i: WHO PEN for primary care in low-resource settings overview*

Goals
To close the gap between what is needed and what is currently available to reduce the burden, health-care costs and human suffering due to major NCDs by achieving higher coverage of essential interventions in LMIC
■ To achieve universal access to high-quality diagnosis and patient-centred treatment ■ To reduce the suffering and socioeconomic burden associated with major NCDs ■ To protect poor and vulnerable populations from heart disease, stroke, hypertension cancer, diabetes, asthma and chronic respiratory disease ■ To provide effective and affordable prevention and treatment through primary care ■ To support early detection, community engagement and self-care

Objectives
Equity and efficiency objectives **Improve the efficiency of care of major NCD in primary care through:**
■ enhanced implementation of human rights standards; ■ provision of cost effective interventions based on need rather than ability to pay; ■ targeting limited resources to those who are most likely to benefit due to high risk; ■ standardization of diagnostic and investigation procedures and drug prescription; ■ formulation of referral criteria for further assessment or hospitalization; ■ definition of parameters for planning and budget; ■ selection of monitoring and evaluation indicators.
Quality of care objectives **Improve the quality of care of major NCD in primary care through:**
■ cost effective case management; ■ appropriate referral and follow-up; ■ prevention, early detection and cost effective case management ■ management of exacerbations and emergencies; ■ follow-up of long-term treatment prescribed by the specialist.
Health impact objectives **Have a beneficial impact on health through:**
■ reduction of tobacco consumption in NCD patients; ■ reduction of the average delay in the diagnosis of NCD by the health services; ■ reduction of the risk of heart attacks, strokes, amputations and kidney failure; ■ reduction of case fatality of major NCDs; ■ prevention of acute events and complications; ■ prolongation of the duration of stable clinical periods for CVDs, diabetes, asthma and COPD patients.

Reference: World Health Organization Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings, World Health Organization, 2010.

Table ii: Contribution of WHO PEN to Health System Building Blocks*

Leadership/governance	■ Assess needs and gaps and facilitate the use of available resources for prevention and control of NCDs efficiently and equitably ■ Support government efforts to drive the agenda towards universal coverage.
Financing	■ Prioritize NCD interventions to support raising of adequate funds for universal coverage ■ Facilitate phased- out provision of financial protection for NCDs.
Medical products and technologies	■ Define prerequisites for integrating a core set of essential NCD interventions into primary care ■ Develop an affordable list of essential medicines and appropriate technologies ■ Improve access to essential medicines.
Health information system	■ Provide templates to gather reliable health information of people
Health workforce	■ Provide training material to enhance knowledge and skills for NCDs prevention and control ■ Audit performance
Service delivery	■ Improve access to essential preventive and curative NCD interventions ■ Provide equitable opportunities for early detection ■ Define core set of cost-effective NCD interventions ■ Provide tools for their implementation ■ Improve quality of care ■ Improve gate-keeper function of primary care ■ Reduce costs due to hospital admissions and complications.
People	■ Develop tools for community engagement and empowerment of people for self-care ■ Improve health outcomes.

Reference: World Health Organization Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings, World Health Organization, 2010.

Table iii: Core set of policy options and cost-effective interventions for prevention and control of major noncommunicable diseases through a primary health care approach*

Objective 4   To strengthen and orient health systems to address the prevention and control of noncommunicable diseases and the underlying social determinants through people-centred primary health care and universal health coverage

- Integrate very cost-effective noncommunicable disease interventions into the basic primary health care package to advance the universal health coverage agenda
- Explore viable health financing mechanisms and innovative economic tools supported by evidence
- Scale up early detection and coverage, prioritizing very cost-effective high-impact interventions
- Train health workforce and strengthen capacity of health system particularly at primary care level

- Improve availability of affordable basic technologies and essential medicines, including generics, required to treat major noncommunicable diseases, in both public and private facilities
- Implement other cost-effective interventions and policy options in objective 4 to strengthen and orient health systems to address noncommunicable diseases and risk factors through people-centred primary health care and universal health coverage.
- Develop and implement a palliative care policy

Cardiovascular disease and diabetes: §

- Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) to individuals who have had a heart attack or stroke and to persons with high risk ($\geq$ 30%) of a fatal and nonfatal cardiovascular event in the next 10 years*
- Acetylsalicylic acid for acute myocardial infarction*
- Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) to individuals who have had a heart attack or stroke, and to persons with moderate risk ($\geq$ 20%) of a fatal and nonfatal cardiovascular event in the next 10 years
- Secondary prevention of rheumatic fever and rheumatic heart disease
- Detection, treatment and control of hypertension
- Acetylsalicylic acid, atenolol and thrombolytic therapy (streptokinase) for acute myocardial infarction
- Treatment of congestive cardiac failure with ACE inhibitor, beta-blocker and diuretic
- Cardiac rehabilitation post myocardial infarction
- Anticoagulation for medium- and high-risk non-valvular atrial fibrillation and for mitral stenosis and atrial fibrillation
- Low-dose acetylsalicylic acid for ischemic stroke

Diabetes: §

- Lifestyle interventions for preventing type 2 diabetes
- Influenza vaccination for patients with diabetes
- Preconception care among women of reproductive age including patient education and intensive glucose management
- Detection of diabetic retinopathy by dilated eye examination followed by appropriate laser photocoagulation therapy to prevent blindness
- Effective angiotensin-converting enzyme inhibitor drug therapy to prevent progression of renal disease
- Care of acute stroke and rehabilitation in stroke units
- Interventions for foot care: educational programs, access to appropriate footwear; multidisciplinary clinics.

Cancer: [§]

- Prevention of liver cancer through hepatitis B immunization*
- Prevention of cervical cancer through screening (visual inspection with acetic acid [VIA] [&] linked with timely treatment of pre-cancerous lesions*
- Vaccination against human papillomavirus, as appropriate if cost-effective and affordable, according to national programmes and policies
- [&&] Population-based cervical cancer screening linked with timely treatment
- [&&] Population-based breast cancer and mammography screening (50-70 years) linked with timely treatment
- [&&] Population-based colorectal cancer screening at age >50, linked with timely treatment
- [&&] Oral cancer screening in high-risk groups (e.g. tobacco users, betel-nut chewers) linked with timely treatment

Chronic respiratory disease: [§]

- Access to improved stoves and cleaner fuels to reduce indoor air pollution
- Cost-effective interventions to prevent occupational lung diseases, e.g. from exposure to silica, asbestos
- Treatment of asthma based on WHO guidelines
- Influenza vaccination for patients with chronic obstructive pulmonary disease

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*   Very cost-effective i.e. generate an extra year of healthy life for a cost that falls below the average annual income or gross domestic product per person

[§]   Policy actions for prevention of major noncommunicable diseases are listed under objective 3

[&]   Or Pap smear (cervical cytology), if very cost-effective

[&&]   Screening is meaningful only if the capacity for diagnosis, referral and treatment is simultaneously improved.

Reference: Global Action Plan for Prevention and Control of Noncommunicable Diseases 2013-2020, Appendix 3.

I. Protocols for primary care

for management of hypertension, diabetes, raised cardiovascular risk, asthma, chronic obstructive pulmonary disease and referral of suspected breast and cervical cancer through an integrated approach

A 25% relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases

At least 50% of eligible people receive drug therapy and counselling (including glycaemic control) to prevent heart attacks and strokes

WHO PEN Protocol 1
Prevention of Heart Attacks, Strokes and Kidney Disease through Integrated Management of Diabetes and Hypertension

When could this Protocol be used?

- The protocol is for assessment and management of cardiovascular risk using hypertension, diabetes mellitus (DM) and tobacco use as entry points
- It could be used for routine management of hypertension and DM and for screening, targeting the following categories of people:
  - age > 40 years
  - smokers
  - waist circumference (≥ 90 cm in women ≥100 cm in men)
  - known hypertension
  - known DM
  - history of premature CVD in first degree relatives
  - history of DM or kidney disease in first degree relatives

Follow instructions given in Action 1 to Action 4, step by step

FIRST VISIT

Action 1. Ask about:

- Diagnosed heart disease, stroke, TIA, DM, kidney disease
- Angina, breathlessness on exertion and lying flat, numbness or weakness of limbs, loss of weight, increased thirst, polyuria, puffiness of face, swelling of feet, passing blood in urine etc
- Medicines that the patient is taking
- Current tobacco use (yes/no) (answer yes if tobacco use during the last 12 months)

- Alcohol consumption (yes/no) (if `Yes`, frequency and amount)
- Occupation (sedentary or active)
- Engaged in more than 30 minutes of physical activity at least 5 days a week (yes/no)
- Family history of premature heart disease or stroke in first degree relatives

FIRST VISIT

Action 2. Assess (physical exam and blood and urine tests):

- Waist circumference
- Measure blood pressure, look for pitting odema
- Palpate apex beat for haeving and displacement
- Auscultate heart (rhythm and murmurs)
- Auscultate lungs (bilateral basal crepitations)
- Examine abdomen (tender liver)
- In DM patients examine feet; sensations, pulses, and ulcers

- Urine ketones (in newly diagnosed DM) and protein
- Total cholesterol
- Fasting or random blood sugar (diabetes= fasting blood sugar≥7 mmol/l (126 mg/dl)) or random blood sugar ≥11.i mmol/l (200 mg/dl))

(Point of care devices can be used for testing blood sugar if laboratory facilities are not available)

Action 3. Estimate cardiovascular risk (in those not referred):

- Use the WHO/ISH risk charts relevant to the WHO subregion (Annex and CD)
- Use age, gender, smoking status, systolic blood pressure, DM (and plasma cholesterol if available)
- If age 50-59 years select age group box 50, if 60-69 years select age group box 60 etc., for people age < 40 years select age group box 40
- If cholesterol assay cannot be done use the mean cholesterol level of the population or a value of 5.2 mmol/l to calculate the cardiovascular risk)

- If the person is already on treatment, use pretreatment levels of risk factors (if information is available to assess and record the pretreatment risk. Also assess the current risk using current levels of risk factors)
- Risk charts underestimate the risk in those with family history of premature vascular disease, obesity, raised triglyceride levels

Action 4: Referral criteria for all visits:

- BP >200/>120 mm Hg (urgent referral)
- BP ≥140 or ≥ 90 mmHg in people < 40 yrs (to exclude secondary hypertension)
- Known heart disease, stroke, transient ischemic attack, DM, kidney disease (for assessment, if this has not been done)
- New chest pain or change in severity of angina or symptoms of transient ischemic attack or stroke
- Target organ damage (e.g. angina, claudication, haeving apex, cardiac failure)
- Cardiac murmurs
- Raised BP ≥140/90 (in DM above 130/80mmHg) while on treatment with 2 or 3 agents

- Any proteinuria
- Newly diagnosed DM with urine ketones 2+ or in lean persons of <30 years
- Total cholesterol >8mmol/l
- DM with poor control despite maximal metformin with or without sulphonylurea
- DM with severe infection and/or foot ulcers
- DM with recent deterioration of vision or no eye exam in 2 years
- High cardiovascular risk

If referral criteria are not present go to Action 5

FIRST VISIT

Action 5. Counsel all and treat as shown below

Risk < 20%

- Counsel on diet, physical activity, smoking cessation and avoiding harmful use of alcohol
- If risk < 10% follow up in 12 months
- If risk 10 - < 20% follow up every 3 months until targets are met, then 6-9 months thereafter

Risk 20 to <30%

- Counsel on diet, physical activity, smoking cessation and avoiding harmful use of alcohol
- Persistent BP ≥ 140/90 mm Hg consider drugs (see below ** Antihypertensive medications)
- Follow-up every 3-6 months

Risk > 30%

- Counsel on diet, physical activity, smoking cessation and avoiding harmful use of alcohol
- Persistent BP ≥ 130/80 consider drugs (see below ** Antihypertensive medications)
- Give a statin
- Follow-up every 3 months, if there is no reduction in cardiovascular risk after six months of follow up refer to next level

Important practice points

Consider drug treatment for following categories

- All patients with established DM and cardiovascular disease (coronary heart disease, myocardial infarction, transient ischaemic attacks, cerebrovascular disease or peripheral vascular disease), renal disease. If stable, should continue the treatment already prescribed and be considered as with risk >30%
- People with albuminuria, retinopathy, left ventricular hypertrophy
- All individuals with persistent raised BP ≥160/100 mmHg; antihypertensive treatment
- All individuals with total cholesterol at or above 8 mmol/l (320 mg/dl); lifestyle advice and statins

** Antihypertensive medications

- If under 55 years low dose of a thiazide diuretic and/ or angiotensin converting enzyme inhibitor
- If over 55 years calcium channel blocker and/or low dose of a thiazide diuretic
- If intolerant to angiotensin converting enzyme inhibitor or for women in child bearing age consider a beta blocker
- Thiazide diuretics and/or long-acting calcium channel blockers are more appropriate as initial treatment for certain ethnic groups. Medications for compelling indications should be prescribed, regardless of race/ ethnicity
- Test serum creatinine and potassium before prescribing an angiotensin converting enzyme inhibitor

Additional actions for individuals with DM:

- Give an antihypertensive for those with BP ≥ 130/80 mmHg
- Give a statin to all with type 2 DM aged ≥ 40 years
- Give Metformin for type 2 DM if not controlled by diet only (FBS>7mmol/l), and if there is no renal insufficiency, liver disease or hypoxia.
- Titrate metformin to target glucose value
- Give a sulfonylurea to patients who have contraindications to metformin or if metformin does not improve glycaemic control.
- Give advise on foot hygiene, nail cutting, treatment of calluses, appropriate footwear and assess feet at risk of ulcers using simple methods (inspection, pin-prick sensation)
- Angiotensin converting enzyme inhibitors and/or low-dose thiazides are recommended as first-line treatment of hypertension. Beta blockers are not recommended for initial management but can be used if thiazides or angiotensin converting enzyme inhibitors are contraindicated.
- Follow up every 3 months

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FIRST VISIT

Advice to patients and family

- Avoid table salt and reduce salty foods such as pickles, salty fish, fast food, processed food, canned food and stock cubes
- Have your blood glucose level, blood pressure and urine checked regularly

Advice specific for DM

- Advise overweight patients to reduce weight by reducing their food intake.
- Advise all patients to give preference to low glycaemic-index foods (e.g.beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet
- If you are on any DM medication that may cause your blood glucose to go down too low carry sugar or sweets with you
- If you have DM, eyes should be screened for eye disease (diabetic retinopathy) by an ophthalmologist at the time of diagnosis and every two years thereafter, or as recommended by the ophthalmologist
- Avoid walking barefoot or without socks
- Wash feet in lukewarm water and dry well especially between the toes
- Do not cut calluses or corns, and do not use chemical agents on them
- Look at your feet every day and if you see a problem or an injury, go to your health worker

SECOND VISIT

Repeat

- Ask about: new symptoms, adherence to advise on tobacco and alcohol use, physical activity, healthy diet, medications etc
- Action 2 Assess (Physical exam)
- Action 3 Estimate cardiovascular risk
- Action 4 Refer if necessary
- Action 5 Counsel all and treat as shown in protocol

References:
Prevention and control of noncommunicable diseases; Guidelines for primary health care, World Health Organization, 2012

Scaling up action against noncommunicable diseases. How much will it cost?, World Health Organization, 2011

Prevention of cardiovascular diseases; Pocket guidelines for assessment and management of cardiovascular risk, World Health Organization, 2008

WHO PEN Protocol 2
Health Education and Counseling on Healthy Behaviours
(to be applied to ALL)

Educate your patient to

- Take regular physical activity
- Eat a "heart healthy" diet
- Stop tobacco and avoid harmful use of alcohol
- Attend regular medical follow-up

Take regular physical activity

- Progressively increase physical activity to moderate levels (such as brisk walking); at least 150 minutes per week
- Control body weight and avoid overweight by reducing high calorie food and taking adequate physical activity

Eat a heart healthy diet

Salt (sodium chloride)
- Restrict to less than 5 grams (1 teaspoon) per day
- Reduce salt when cooking, limit processed and fast foods

Fruits and vegetables
- 5 servings (400-500 grams) of fruits and vegetable per day
- 1 serving is equivalent to 1 orange, apple, mango, banana or 3 tablespoons of cooked vegetables

Fatty food
- Limit fatty meat, dairy fat and cooking oil (less than two tablespoons per day)
- Replace palm and coconut oil with olive, soya, corn, rapeseed or safflower oil
- Replace other meat with chicken (without skin)

Stop Tobacco and avoid harmful use of Alcohol:

- Encourage all non-smokers not to start smoking
- Strongly advise all smokers to stop smoking and support them in their efforts
- Individuals who use other forms of tobacco should be advised to quit
- Alcohol abstinence should be reinforced.
- People should not be advised to start taking alcohol for health reasons
- Advise patients not to use alcohol when additional risks are present, such as:
  - driving or operating machinery
  - pregnant or breast feeding
  - taking medications that interact with alcohol
  - having medical conditions made worse by alcohol
  - having difficulties in controlling drinking

Adherence to treatment

- If the patient is prescribed a medicine/s:
  - teach the patient how to take it at home:
  - explain the difference between medicines for long- term control (e.g. blood pressure) and medicines for quick relief (e.g. for wheezing)
  - tell the patient the reason for prescribing the medicine/s
- Show the patient the appropriate dose
- Explain how many times a day to take the medicine
- Label and package the tablets
- Check the patient's understanding before the patient leaves the health centre
- Explain the importance of:
  - keeping an adequate supply of the medications
  - the need to take the medicines regularly as advised even if there are no symptoms

A1: ASK	Do you use tobacco?	→ NO →	Reinforce message that tobacco increases risk of heart disease

A2: ADVISE	YES →	**Advise to quit in a clear, strong and personalized manner** "Tobacco use increases the risk of developing a heart attack, stroke, lung cancer and respiratory diseases. Quitting tobacco use is the **one most important thing** you can do to protect your heart and health, you have to quit now."

A3: ASSESS	Are you willing to make a quit attempt now ?

YES   NO

A4: ASSIST	**Assist in preparing a quitting plan** Set quit date Inform family and friends Ask for their support Remove cigarettes/tobacco Remove objects/articles that prompt you to smoke Arrange follow up visit*	**Promote motivation to quit** Provide information on health hazards of tobacco and give leaflet to the patient

A5: ARRANGE	**At follow-up visit** Congratulate success and reinforce If patient has relapsed, consider more intensive follow-up and support from family

* Ideally second follow-up visit is recommended within the same month and every month thereafter for 4 months and evaluation after 1 year. If not feasible, reinforce counseling whenever the patient is seen for blood pressure monitoring.

WHO PEN Protocol 3
3.1 Management of Asthma
3.2 Management of Chronic Obstructive Pulmonary Disease (COPD)

ASK	Asthma and COPD can both present with cough, difficult breathing, tight chest and/or wheezing

DIAGNOSIS	The following features make a diagnosis of asthma more likely: ■ previous diagnosis of asthma; ■ symptoms since childhood or early adulthood; ■ history of hayfever, eczema and/or allergies; ■ intermittent symptoms with asymptomatic periods in between; ■ symptoms worse at night or early morning; ■ symptoms triggered by respiratory infection, exercise, weather changes or stress; ■ symptoms respond to salbutamol.	The following features make a diagnosis of COPD more likely: ■ previous diagnosis of COPD; ■ history of heavy smoking, i.e. >20 cigarettes per day for >15 years; ■ history of heavy and prolonged exposure to burning fossil fuels in an enclosed space, or high exposure to dust in an occupational setting; ■ symptoms started in middle age or later (usually after age 40); ■ symptoms worsened slowly over a long period of time; ■ long history of daily or frequent cough and sputum production often ■ starting before shortness of breath; ■ symptoms that are persistent with little day-to-day variation.

TEST	Measure Peak Expiratory Flow rate (PEFR) ■ Give two puffs of salbutamol and remeasure in 15 minutes ■ If the PEF improves by 20%, a diagnosis of asthma is very probable. ■ Smaller response makes a diagnosis of COPD more likely

Reference: *Guidelines for primary health care in low resource settings Management of asthma and chronic obstructive pulmonary disease*. World Health Organization, 2012

WHO PEN Protocol 3.1
Management of Asthma

ASK	**Is asthma well controlled or uncontrolled?**

Asthma is considered to be well controlled if the patient has:
- daytime asthma symptoms and uses a beta agonist two or fewer times per week;
- night time asthma symptoms two or fewer times per month;
- no or minimal limitation of daily activities;
- no severe exacerbation (i.e. requiring oral steroids or admission to hospital) within a month;
- a PEFR, if available, above 80% predicted.

If any of these markers are exceeded, the patient is considered to have uncontrolled asthma.

TREAT	**Increase or decrease treatment according to how well asthma is controlled using a stepwise approach**

Step 1. Inhaled salbutamol prn
Step 2. Inhaled salbutamol prn plus low-dose inhaled beclometasone, starting with 100ug twice daily for adults and 100ug once or twice daily for children
Step 3. Same as step 2, but give higher doses of inhaled beclometasone, 200ug or 400ug twice daily
Step 4. Add low-dose oral theophylline to Step 3 treatment (assuming long-acting beta agonists and leukotriene antagonists are not available)
Step 5. Add oral prednisolone, but in the lowest dose possible to control symptoms (nearly always less than 10mg daily)

At each step, check the patient's adherence to treatment and observe their inhaler technique.

REFER	**Review asthma control every 3-6 months and more frequently when treatment has been changed or asthma is not well controlled.**

Referral for specialist:
- when asthma remains poorly controlled;
- when the diagnosis of asthma is uncertain;
- when regular oral prednisolone is required to maintain control.

WHO PEN Protocol 3.1
Management of exacerbation of Asthma

ASSESS	**Assess severity**

Severe
- PEFR 33-50% best or predicted.
- Respiratory rate more than 25 breaths/minute (adult).
- Heart rate ≥110 beats/minute.(adult)
- Inability to complete sentences in one breath.

Very severe
altered conscious level, exhaustion, arrhythmia, hypotension, cyanosis, silent chest, poor respiratory effort.
- SpO2 <92%

TREAT	**First-line treatment**	**Second-line treatment to be considered if the patient is not responding to first-line treatment**

First-line treatment

- prednisolone 30–40mg for five days for adults and 1mg per kg for three days for children, or longer, if necessary, until they have recovered;
- salbutamol in high doses by metered dose inhaler and spacer (e.g. four puffs every 20 minutes for one hour) or by nebulizer;
- oxygen, if available, and if oxygen saturation levels are low (below 90%).

Reassess at intervals depending on severity.

Second-line treatment to be considered if the patient is not responding to first-line treatment

- Increase frequency of dosing via an metered dose inhaler and spacer or by nebulizer, or give salbutamol by continuous nebulization at 5–10mg per hour, if appropriate nebulizer available;
- for children, nebulized ipratropium, if available, can be added to nebulized salbutamol.

ADVICE	**Asthma - Advice to patients and families**

Regarding prevention:
- avoid cigarette smoke and trigger factors for asthma, if known;
- avoid dusty and smoke-filled rooms;
- Avoid occupations that involve agents capable of causing occupational asthma
- reduce dust as far as possible by using damp cloths to clean furniture, sprinkling the floor with water before sweeping, cleaning blades of fans regularly and minimizing soft toys in the sleeping area;
- It may help to eliminate cockroaches from the house (when the patient is away) and shake and expose mattresses, pillows, blankets, etc. to sunlight.

Regarding treatment, ensure that the patient or parent:
- knows what to do if their asthma deteriorates;
- understands the benefit from using inhalers rather than tablets, and why adding a spacer is helpful;
- is aware that inhaled steroids take several days or even weeks to be fully effective.

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WHO PEN Protocol 3.2
Management of Chronic Obstructive Pulmonary Disease

ASSESS	**Assess severity**
	Moderate - if breathless with normal activity
	Severe - if breathless at rest
	Measure PEFR and oxygen saturation, if possible.

TREAT	■ inhaled salbutamol, two puffs as required, up to four times daily; ■ if symptoms are still troublesome, consider low-dose oral theophylline; ■ if ipratropium inhalers are available, they can be used instead of, or added to, salbutamol, but they are more expensive.

ADVICE	**COPD - Advice to patients and families**
	■ ensure they understand that smoking and indoor air pollution are the major risk factors for COPD – therefore, patients with COPD must stop smoking and avoid dust and tobacco smoke; ■ keep the area where meals are cooked well ventilated by opening windows and doors; ■ cook with wood or carbon outside the house, if possible, or build an oven in the kitchen with a chimney that vents the smoke outside; ■ stop working in areas with occupational dust or high air pollution – using a mask may help, but it needs to have an appropriate design and provide adequate respiratory protection.

Management of exacerbation of COPD

TREAT	■ antibiotics should be given for all exacerbations; ■ for severe exacerbations, give oral prednisolone 30–40mg for around seven days; ■ give high doses of inhaled salbutamol by nebulizer or metered dose inhaler with spacer; (e.g. four puffs every 20 minutes for one hour) or by nebulizer; ■ oxygen, if available, should be given by a mask that limits the concentration to 24% or 28%.

WHO PEN Protocol 4
4.1 Assessment and referral of women with suspected breast cancer at primary health care

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Women who present the following persistent and unexplained signs and symptoms should seek consultation at a PHC:

a) Breast lump, or any change in the shape or consistency of the breast

b) Breast lump that enlarges and/or is fixed and hard

c) Other breast problems (i.e. eczematous skin changes, nipple retraction, peau d'orange, ulceration, unilateral nipple discharge – particularly bloody discharge –, lump in the axilla) with or without palpable lump

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Assess likelihood for breast cancer

- Assess signs and symptoms (i.e. history, intensity, duration, progression)
- Identify relevant breast cancer risk factors (such as age, family history, previous history of breast cancer, chest irradiation)
- Clinical examination of both breasts, axillae and neck
- Differential diagnosis: benign breast diseases (e.g. fibroadenoma, fibroadenosis, mastitis, abscess, etc.)

Women < 30 years old

Women 30 years old and above

Presenting with a)

Presenting with:

a) + relevant risk factors, or

b) or c)

Presenting with:

a) b) or c)

Invite for follow-up visit after menstrual period

Follow-up visit: if b) or c)

Refer immediately to next level

Note:

Referral of women with small breast lumps may lead to diagnosis of "early breast cancer"

WHO PEN Protocol 4
4.2 Assessment and referral of women with suspected cervical cancer at primary health care

Women who present the following persistent and unexplained signs and symptoms should seek consultation at a PHC:

a) Abnormal vaginal bleeding (i.e. after coitus, between menstrual periods, post menopause)

b) Foul-smelling discharge

c) Pain during vaginal intercourse

d) Any of the above associated with palpable abdominal mass with persistent low back or abdominal pain

↓

Assess likelihood for cervical cancer

- Assess signs and symptoms (i.e. history, intensity, duration, progression)
- Identify relevant risk factors: age (30 years old and above)
- Speculum examination
- Differential diagnosis: abortion in pre-menopausal women, infections (e.g. Chlamydiae, gonococcal, etc.), genital ulcers, cervical inflammation, uterine polyps, dysfunctional uterus hemorrhage, endometrial or vaginal cancer

| **Women presenting with a) b) or c)** | **Women presenting with d)** |

Without clinically detected cervical growth or ulceration

With clinical detected cervical growth or ulceration

Follow obstetric and gynecological guidelines as appropriate

Refer if condition is not manageable at PHC, persists or worsens

Refer immediately to next level

Note: *Referral of women with a) b) or c) may lead to a diagnosis of "early invasive cervical cancer", particularly in women* **30 years old and above.**

Reference: *Guidelines for referral of suspected breast and cervical cancer at primary health care in low resource settings,* World Health Organization, 2013

Essential technologies and tools for implementing essential NCD interventions in primary care

Technologies	Tools
Thermometer	WHO/ISH risk prediction charts
Stethoscope	Evidence based clinical
Blood pressure measurement device*	protocols
Measurement tape	Flow charts with referral criteria
Weighing machine	Patient clinical record
Peak flow meter**	Medical information register
Spacers for inhalers	Audit tools
Glucometer	
Blood glucose test strips	
Urine protein test strips	
Urine ketones test strips	
Add when resources permit:	
Nebulizer	
Pulse oximeter	
Blood cholesterol assay	
Lipid profile	
Serum creatinine assay	
Troponin test strips	
Urine microalbuminuria test strips	
Tuning fork	
Electrocardiograph (if training to read and interpret electrocardiograms is available)	
Defibrillator	

* For facilities with nonphysician health workers a validated blood pressure measurement device with digital reading is preferable for accurate measurement of blood pressure (28, 29)

** Disposable mouth pieces required. Peak flow meters with one-way flow preferable.

Reference:
Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings, World Health Organization, 2010.

Core list of medicines required for implementing essential NCD interventions in primary care

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For Primary Care facilities with Physicians

(for PC facilities with only non-physician health workers most of the medicines below are required for refill of prescriptions issued by physicians at a higher level of care)

Thiazide diuretic	Ibuprofen
Calcium channel blocker (long acting) (amlodipine)	Codeine
	Morphine
Beta-blocker	Penicillin
Angiotensin converting enzyme inhibitor (long acting)	Erythromycin
	Amoxicillin
Statin	Hydrocortisone
Insulin	Epinephrine
Metformin	Heparin
Glibenclamide	Diazepam
Isosorbide dinitrate	Magnesium sulphate
Glyceryl trinitrate	Promethazine
Furosemide	Senna
Spironolactone	Dextrose infusion
Salbutamol	Glucose injectable solution
Prednisolone	Sodium chloride infusion
Beclometasone	Oxygen
Aspirin	
Paracetamol	

References:

WHO model list Essential Medicines 17th edition, World Health Organization.

Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings, World Health Organization, 2010.

Aspirin, thiazide diuretic, calcium channel blocker, ACE inhibitor, betablocker, statin and metformin are essential to reach the target on prevention of heart attacks strokes and diabetes complications.

II. Guidelines and other implementation tools

Guidelines for referral of suspected breast and cervical cancer at primary health care in low-resource settings

Abbreviations

GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPV	Human papillomavirus
IARC	International Agency for Research on Cancer
PHC	Primary Health Care
PPV	Positive predictive value
NCD	Noncommunicable disease
NMH	Noncommunicable Diseases and Mental Health
SIR	Standardized incidence rate
WHO	World Health Organization

Executive Summary

The *Guidelines for referral of suspected breast and cervical cancer at primary health care in low resource settings* are part of a set of referral guidelines that also include colorectal, oral, and prostate cancer. Moreover, these referral guidelines for five cancer sites belong to a broader set of guidelines for essential interventions for noncommunicable diseases (NCDs). Their intended use is for primary health-care physicians, nurses, and other health-care practitioners at Primary Health Care (PHC) in resource-constrained settings, where the majority of cancer cases are diagnosed in late stages.

The primary objective of these guidelines is to guide primary care practitioners in the early identification of patients with signs and symptoms suspicious of breast and cervical cancer so they can be immediately referred to the next level of care for diagnosis and subsequent treatment, if cancer is confirmed .

The application of these guidelines at PHC requires raising awareness on the early symptoms and signs of breast and cervical cancer among the general population and encouraging target women to seek prompt attention at PHC centres. It also requires adequate access to specialized diagnostic and treatment services for referral cases. Due to the brief nature of the guidelines, they can be easily and widely disseminated for day-to-day use by PHC practitioners. It is expected that the implementation of these guidelines will contribute to increasing the percentage of cases diagnosed in the early stages of disease in the short-term, as well as increasing survival rates and reducing mortality from breast and cervical cancer in the medium- and long-term.

In the case of cervical cancer, the guidelines target the detection of invasive cervical cancer in early clinical stages and are complementary to the objectives of the WHO guidelines titled *Comprehensive cervical cancer control — A guide to essential practice* (C4GEP). As stated in C4GEP, organized population-based screening of women over 30 years of age is the key early detection strategy that can reduce the incidence and mortality of invasive cervical cancer in a significant way. However, in those settings where cervical cancer screening is not yet available or is in its initial stages of development, prompt referral based on symptoms and signs is the only other method of diagnosing cervical cancer in earlier stages when treatment is more effective. It is also important to keep in mind that even in well-established cervical screening programmes there are women who will present with an invasive cancer that can be detected early through warning signs and symptoms. These are mainly women who do not receive screening, as well as women who, although regularly screened, may have a false negative result or develop an interval cancer.

These guidelines were developed according to the WHO process for guideline development. They include recommendations for referral to the next level of care and are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, and the Guideline Development Group (GDG) considerations.

Women aged 30 years and older have the highest risk of developing breast or cervical cancer, whereas these cancer types are comparatively rare in women under this age (GLOBOCAN, 2008; Ferlay *et al*. 2010). Therefore, the GDG decided to provide, as appropriate, distinct recommendations according to the different age groups and ensure the focus is on women at risk. Otherwise there is a danger of a dramatic increase of false positives from women under 30 years of age with unnecessary overload of the health system.

Most of the evidence for signs and symptoms was assessed as low quality (see Grade Tables in Annex I). However, based on GDG clinical considerations, and the high value placed by all GDG members in detecting cancer in earlier stages, the following are strong recommendations for referral of women with possible breast and cervical cancer:

Breast cancer

- Women who report any breast symptoms at PHC should undergo physical examination of both breasts, both axillae, and the neck prior to referral.

- Women with a palpable breast lump, unilateral spontaneous nipple discharge (particularly bloody discharge) , or any change in the shape, consistency, or density of the breast, whether associated with other symptoms or risk factors, should be referred to a facility where diagnosis, staging, and treatment of breast cancer can be efficiently carried out as indicated below:

  - Women **aged 30 years and older** with a breast lump, spontaneous unilateral nipple discharge (particularly bloody discharge), skin changes such as eczematous changes in or around the nipple or areola, skin tethering, and skin or nipple retraction should be referred for further investigations to rule out breast cancer

  - Women **under the age of 30 years** with a breast lump should only be referred for further investigation if the lump enlarges or has other features associated with cancer (such as fixed or hardness or the presence of skin changes) or in whom there are other reasons for concern, such as a family history of breast cancer, former breast cancer, or prior therapeutic chest irradiation.

- Women with any other symptoms highly indicative of advanced breast cancer (such as a large lump in the breast, skin ulceration,

axillary swelling, palpable axillary nodes, swelling in the neck, severe back pain) should also be referred to a specialized centre for diagnosis and appropriate care.

■ Women found with no abnormalities upon physical examination should be taught breast awareness. This comprises educating women on breast cancer signs and symptoms, encouraging them to be aware of their normal breast and of any changes by periodic self-palpation, as well as empowering them to seek care promptly in case of any future breast abnormalities.

Cervical cancer

■ Women who report at PHC any gynaecological sign or symptom suspicious of early cervical cancer (such as abnormal vaginal bleeding,[1] persistent, foul-smelling discharge, or pain during vaginal intercourse) should, where possible, undergo a speculum examination. The following important issues should be taken into consideration:

■ In women with abnormal vaginal bleeding, with persistent, foul-smelling discharge, or experiencing pain during vaginal intercourse, the **presence of a cervical growth or ulceration** should prompt immediate referral for diagnostic confirmation and management without manipulation because of the significant risk of bleeding, which may be difficult to control.

■ Women with abnormal vaginal bleeding, with persistent, foul-smelling discharge, or experiencing pain during vaginal intercourse, **without clinically detected cervical growth or ulceration**, are likely to have a non-malignant condition, particularly if they are under 30 years old. These women should be treated as appropriate[2] and be referred to a specialist to rule out cervical cancer only if the condition persists or has worsened at the time of a follow-up visit.

■ In making a recommendation for further investigation, it should be emphasized that the likeliest possibility is that vaginal bleeding, persistent, foul-smelling discharge, or pain during vaginal intercourse with or without clinically detected cervical growth or ulceration are not caused by a cancer. However, it is important to undergo further investigation because, in the event that cancer is

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1 Abnormal vaginal bleeding includes occurrences after coitus, between menstrual periods, or after menopause.

2 For further information, consult the following WHO guidelines: *WHO Guidelines for the Management of Sexually Transmitted Infections* (WHO 2003) and *Managing Complications in Pregnancy and Childbirth: a guide for midwives and doctors* (WHO 2000).

diagnosed, the treatment outcome is much better when the cancer is detected early and treated properly. This is particularly relevant in women 30 years and older who are at higher risk of developing cervical cancer.

■ Women with any signs or symptoms associated with advanced cervical cancer (such as severe abdominal pain, abdominal distension, severe back pain, neck swelling, or symptoms of urethral and rectal fistula) should also be referred to a specialized centre for confirmation diagnosis and appropriate care.

Introduction

The Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) 2013-2020, endorsed by the World Health Assembly in May 2013, (WHO, 2013) calls upon WHO to provide technical guidance to countries for the integration into their health systems of cost-effective interventions against major NCDs. This includes the early detection of cancer. In low-resource settings where the majority of patients present in late stages, there is a general lack of early detection programmes.

Early detection comprises two strategies: *screening* and *early diagnosis*. **Screening** is the systematic application of a screening test for a specific cancer in asymptomatic population. **Early diagnosis** (also known as downstaging) is based on improved public and professional awareness (particularly at the PHC level) of signs and symptoms associated with cancer, improved health-care seeking behaviour, and prompt clinical assessment and early referral of suspected cancer cases such that *appropriate* diagnostic investigations and treatment can be rapidly instituted leading to improved survival outcomes with minimal morbidity and cost.

In low-resource settings, more than 80% of breast and cervical cancers are diagnosed in locally advanced stages or with distant metastases. Therefore, in countries that have very limited health system capacity, the overall 5-year survival rate is dismally low, with a range between 10 to 40%. On the other hand, the 5-year survival rate for early, localized breast and cervical cancers exceeds 80% in settings where basic treatment is available and accessible (Ferlay *et al.* 2010; Sankaranarayanan *et al.* 2010 and 2011). Thus, early diagnosis of cancer is initially a very suitable and affordable strategy for early detection and is complementary to screening strategies, when available. Screening is a much more complex public health undertaking than early diagnosis and can be cost-effective when the adequate health system capacity has been achieved and screening coverage has reached over 70% of the target group (WHO, 2007).

The *Guidelines for referral of suspected breast and cervical cancer at primary health care in low resource settings* are part of a broader set of guidelines for essential interventions for NCDs targeting primary health-care providers, such as physicians, nurses, and other health-care practitioners, at PHC facilities in resource-constrained settings (WHO, 2011). Early stages of breast and cervical cancer can be more effectively treated than those in advanced stages, through the use of more affordable and less aggressive therapeutic options with fewer side effects, complications and, as a result, enhanced quality

of life. The survival and mortality outcomes for breast and cervical cancer improved significantly in developed countries much before the introduction of organized screening thanks to improved awareness, clinical diagnosis, and adequate treatment in health services (Sparen *et al.* 1995; Ponten *et al.* 1995; Lim *et al.* 2009).

The lack of awareness among PHC practitioners is a major factor resulting in delayed referral and detection of disease in advanced stages (Thongsuksai *et al.* 2000, Clegg-Lampley *et al.* 2009, Vandborg *et al.* 2011). Therefore, these guidelines are aimed at improving the skills of PHC providers in suspecting possible breast and cervical cancer followed by immediate referral of cases with clinical characteristics consistent with the possibility of cancer to a secondary or tertiary care facility. This is fundamental to an early detection strategy aimed at earlier clinical diagnosis. The current guidelines assume that there is enough capacity in health services to provide adequate diagnosis, treatment, and follow-up care.

Due to the fact that cancer treatment is provided only if diagnosis of cancer is confirmed, the benefits of referring symptomatic women for further investigations outweigh the harms that might result from unnecessary diagnostic tests done in false positive cases. Evidence-based guidelines for referral of patients with suspected cancer at the PHC level have so far not been developed by WHO or by any low- or middle-income country with a wide participation by different stakeholders. A systematic review of the symptoms, signs, and risk factors associated with early diagnosis of breast and cervical cancer provides a valuable basis on which to formulate pragmatic, easy-to-use guidelines for primary care practitioners.

In the case of cervical cancer, the guidelines target the detection of invasive cervical cancer in early clinical stages and are, therefore, complementary to the objectives of *Comprehensive cervical cancer control — A guide to essential practice* (C4GEP). As stated in C4GEP, organized population-based screening of women over 30 years of age is the key early detection strategy that can reduce the incidence and mortality of invasive cervical cancer in a significant way. However, in those settings where cervical cancer screening is not yet available or is in its initial stages of development, prompt referral based on symptoms and signs is the only other method of diagnosing cervical cancer in earlier stages when treatment is more effective. It is also important to keep in mind that even in well-established cervical screening programmes there are women who will present with an invasive cancer that can be detected early through warning signs and symptoms. These are mainly women who do not attend screening, as well as women who, although regularly screened, may have a false negative result or develop an interval cancer.

These guidelines may be used as a resource for self-education of PHC practitioners in low-resource countries to improve their awareness of symptoms and signs of breast and cervical cancers and to empower them to promptly refer suspected cancer cases leading to early detection in routine health-care services. Countries may also use these guidelines as part of national cancer control programmes to reduce the burden of breast and cervical cancer. Countries may adopt the guidelines as such or modify them to suit their local needs.

While implementing the guidelines, countries should be encouraged to develop a set of evaluation measures to assess the impact of the guidelines. Alternatively, countries may implement the guidelines in carefully designed pilot demonstration programmes or operational research projects covering specified target areas thereby permitting accurate evaluation of the feasibility and the outcomes. This will better inform broader, nationwide scaling up of breast and cervical cancer early detection services. Such operational research programmes will be very useful in filling knowledge gaps in the implementation of affordable public health interventions to improve breast and cervical cancer control in low-resource settings. Furthermore, the guidelines can be incorporated in medical, nursing, and health worker training curricula.

Objectives, scope, and methods

The objective of this guideline is to assist primary care practitioners in the early identification of patients with signs and symptoms suspicious of breast and cervical cancer so they can be referred to the next level of care for diagnosis and subsequent treatment, if cancer is confirmed .

The initial scope of the original cancer guidelines, as agreed by the Guideline Development Group (GDG), included breast, cervical, oral, prostate, and colorectal cancer in view of their high incidence in low- and middle-income countries and because they are particularly amenable to early detection and effective treatment. A review of systematic reviews of signs, symptoms, and risk factors for each of the cancer sites was performed and discussed at the first meeting of the GDG in February 2011. In view of the enormous amount of work that the review of five cancer sites involved, the GDG advised to focus initially on breast and cervical cancer, and subsequently on the remaining cancer sites.

A second report[3] was developed that was largely derived from reviews of reviews, because of the very large amount of available data. This review was confined to breast and cervical cancer and focused on three key elements: (1) clinical prediction rules for referring a woman with suspected cancer to specialized services; (2) systematic reviews of signs and symptoms; and (3) systematic reviews of risk factors which have been shown by meta-analyses to be associated with a relative risk or odds ratio above 2.0 for the particular cancer and that are relevant to consider in a low-resource primary health-care setting.[4]

Evidence profiles using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) were constructed for signs, symptoms, and risk factors as follows (see GRADE tables in Annex I):

■ Breast cancer: Breast lump; bloody nipple discharge; previous history of breast cancer; family history of breast cancer; number of first degree relatives with breast cancer in women aged 40-49 years; age at diagnosis of first degree relatives with breast cancer in women aged 40-49 years; history of goiter; and surgically excised fibroadenoma.

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3   Report on evidence review can be found at: http://www.who.int/cancer/publications/en/index.html

4   For example, breast density has a RR >2 for breast cancer, however it requires access to mammography which is quite unlikely to happen at PHC in low-resource countries. Therefore, it was not included in the GRADE analysis.

■ Cervical cancer: Post-coital bleeding; number of sexual partners; age at first intercourse; age at first baby; human papillomavirus (HPV) positive and HPV positive (by DNA test).

Evidence profiles were not prepared for signs, symptoms, and risk factors where there was a lack of evidence or adequate information that could not be retrieved. This includes clinical prediction rules for which limited and inconclusive research was found for breast cancer, and no studies at all were identified for cervical cancer.

Based on the evidence review, a core group of members of the GDG drafted the recommendations which were discussed by all members of the GDG via teleconference on two occasions and later agreed upon by email exchange. There were only minor disagreements in content that were discussed within the group and the final decision was based on what the majority of the GDG members agreed upon. The revised document was sent to four peer reviewers, three of whom provided feedback. The peer reviewers supported the guideline recommendations and provided only minor comments that were incorporated by GDG as appropriate. In addition, an internal review process was carried out under the guidance of the GRC Secretariat, following a GRC request to ensuring consistency with other existing WHO guidelines. Once the internal review was considered completed by the GRC Secretariat, a revised document was sent to GDG for final review and approval. There was general agreement by the GDG on the modifications suggested by the internal review, excepting the removal of algorithms. The majority of GDG members thought the algorithms were useful and should be kept. The final version of the recommendations was approved by consensus. An update of the review was carried out following a request from GRC. The results of the review did not affect the recommendations previously agreed by the GDG.

Declaration of Interest

All external participants, previous to their inclusion in the review groups, signed the WHO standard declaration of interest form and none of them disclosed any relevant interests.

Format, dissemination and implementation

These guidelines, subsidiary products in the form of leaflets or brochures, plus the results of the systematic reviews, will be available on the WHO website. They will also be disseminated in a printed format and will be available in at least three official languages. The guidelines can be adapted and implemented in low-income countries willing to improve cervical and breast cancer early detection in the context of integration of NCD essential interventions into primary care services. They will will be updated within the next 5 years as it is intended to evolve in response to new knowledge, evidence- based information, national needs and experience.It is advised that the application of these guidelines at the PHC level be complemented by raising awareness about breast and cervical cancer among target women and encouraging them to seek prompt attention at PHC centres through public education programmes. Public health services should have adequate facilities and access to diagnostic and treatment services for referred cases. Although the main intention of the guidelines is to contribute to early diagnosis and curative treatment, an important proportion of women will still be picked up in late stages. Therefore, palliative care should be made available to women diagnosed with late stage cancer or women with progressive disease who do not respond to curative treatment.

Figure 1 describes the breast and cervical cancer early diagnosis system with its main components in each level of care.

Evaluation

WHO will work with countries to evaluate the impact of the guidelines by coordinating efforts and providing advice and practical support.[5] It is expected that the implementation of these guidelines will contribute to increase the percentage of cases diagnosed in early stages in the short-term, as well as prolong survival and reduce mortality from breast and cervical cancer in the medium- and long-terms.

The effect of the guidelines will be assessed initially in countries through process indicators, including number of low-resource countries that:

■ Adopt the guidelines as part of stand-alone breast and cervical cancer control programmes;

■ Incorporate and implement guidelines through their national cancer control programmes or as part of the package of essential interventions for noncommunicable diseases;

■ Develop further tools to implement the guidelines;

■ Develop evaluation systems; and

■ Incorporate the guidelines as part of medical, nursing, and health worker training curricula.

Depending on resources, further assistance will be provided to countries in order to monitor outcome indicators such as stage distribution, treatment completion rates, survival, and mortality. Countries should be encouraged to develop hospital-based and/or population-based information systems, including medical records departments and/ or cancer registries to provide the above-stated outcome measures.

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5 For a comprehensive monitoring and evaluation framework see *Cancer Control. Knowledge into Action. WHO Guide for effective programmes. Early Detection*, WHO, 2007. Available at: http://whqlibdoc.who.int/publications/2007/9241547338_eng.pdf.

Figure 1 : Breast and Cervical cancer early diagnosis system
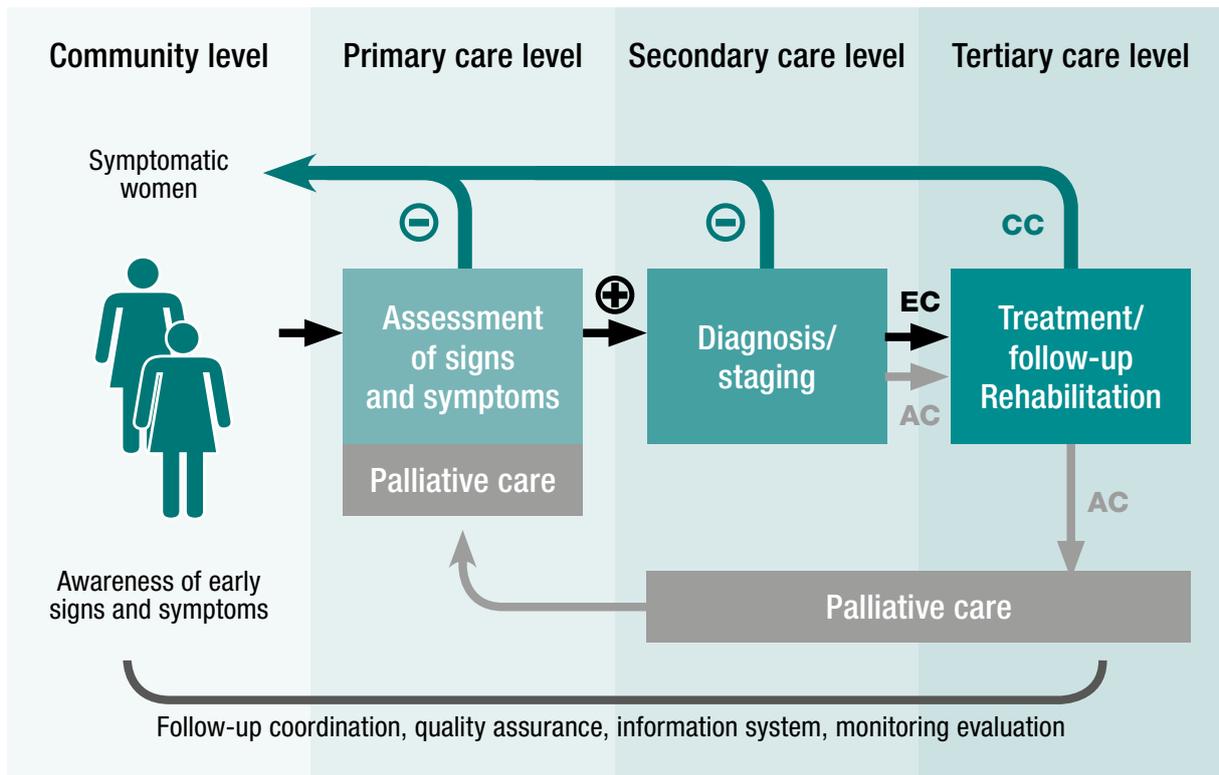
CC Cured cancer   **EC** Early cancer   **AC** Advanced cancer
⊕ Suspected cancer   ⊖ Normal or benign condition

Evidence and recommendations

When presenting the evidence-based guidelines for referral of breast and cervical cancer at PHC in low-resource settings, it is important to highlight the following:

■ The evidence review provides a comprehensive and up-to-date summary of research to underpin the GDG recommendations. However, there is a general lack of research in this area, particularly prospective studies involving long-term follow-up of people with different signs and symptoms. This affects the quantity and quality of the evidence. Moreover, randomized trials that evaluate the clinical predictive value of different signs and symptoms are neither feasible nor ethically acceptable. The clinical predictive value of different signs and symptoms in the early diagnosis of cancer has been predominantly studied in the context of case series, which in the hierarchy of studies provides the lowest quality of evidence.

■ However, clinical predictability based on symptoms, signs and clinical examination is the most important element leading to specific diagnostic algorithms and hence for deciding on referral of patients with suspected breast or cervical cancer to specialized services.

■ Women aged 30 years and above have the highest risk of developing breast or cervical cancer, whereas these cancer types are comparatively rare in women under this age (GLOBOCAN, 2008; Ferlay *et al.* 2010). Therefore, the GDG decided to provide distinct recommendations, as appropriate, according to the different age groups and ensure the focus is on women at risk. Otherwise there is a danger of a dramatic increase of false positives from women under 30 years of age with an unnecessary overload of the health system.

■ The GDG concluded that the existence or absence of risk factors for breast and cervical cancer, in general, do not affect the decision of referral. For an important proportion of women presenting with signs and symptoms suspicious of breast or cervical cancer, specific risk factors may not be identified. Moreover, clinical prediction rules based on combinations of signs, symptoms, and risk factors are not more likely to be useful for deciding on referral than clinical signs and symptoms alone.

■ In view that, in general, risk factors (see Annex II) do not influence the referral of breast or cervical cancer at PHC, GDG decided to not include risk factors in the formulation of the recommendations, except age for both cancers and relevant risk factors for breast cancer (family history, former breast cancer, therapeutic chest irradiation) in women under 30 years of age presenting with a breast lump.

- In some cultures, women presenting with signs and symptoms related to breast or cervical cancer might require a female health-care practitioner to do their clinical assessment.

- Cancer is a life threatening and relatively rare disease. A large proportion of referred patients may not have the suspected cancer on further assessment. Thus, false positive referrals cannot be avoided, but with timely feedback from the referral level, and improved skills in clinical assessment false positive referrals may be reduced.

- The GDG concluded that the benefits of referring symptomatic women for diagnosis of breast and cervical cancer in earlier clinical stages clearly outweighs the harms associated with false positive referrals. GDG also acknowledges the fact that false positive referrals predominantly lead to further diagnostic investigations and patient anxiety until diagnosis of cancer is excluded, but does not entail anti-cancer treatment, as this treatment is initiated only after cancer is confirmed.

An optimal communication strategy is essential to inform women with suspected malignancy that the clinical assessment done at PHC does not constitute a diagnosis, and that there is the need for further investigation to rule out cancer. In talking with the patient, the health-care practitioner should ensure that the anxiety associated with referrals is kept at the lowest possible level.

Referral of women with suspected breast cancer

What are the signs and symptoms in women presenting at PHC that could lead to referral of suspected breast cancer to specialized services?

Breast lump

GRADE evaluation:

The positive predictive value (PPV) of breast lumps for breast cancer varied between 8.1 (95% CI: 6.3% to 10.3%) for a lump to 24.6% (95% CI: 15.2% to 37.1%) for a clinically-palpable lump. The quality of evidence from these studies was graded as low (see GRADE Table 1 in Annex I).

Bloody nipple discharge

GRADE evaluation:

Meta-analyses produced estimates for the odds ratio of breast cancer associated with blood nipple discharge versus other discharge descriptions: bloody vs. non-bloody: 2.27 (95% CI: 1.32-3.89); bloody vs. serous: 2.49 (95% CI: 1.25-4.93); bloody vs. colored: 2.00 (95% CI: 0.74-5.45). The quality of the studies was graded low (see GRADE Table 1 in Annex)

GDG considerations:

Breast lump is a cardinal symptom and sign that may lead to a diagnosis of breast cancer (Mahoney *et al.*, 1982; Aiello *et al.*, 2004; Pradhan *et al.*, 2008; Obene-Yeboah *et al.*, 2008). Prompt referral of any women with a breast lump may lead to early diagnosis of breast cancer with improvement in treatment outcome. Breast lumps of 1 cm diameter or more are generally considered readily palpable by health-care workers, although breast lumps of 5 mm may be palpable (Mahoney *et al.*, 1982; Reintgen *et al.*, 1993).

Discrete lumps with a hard consistency, lumps with eczematous skin changes, lumps with skin tethering or nipple retraction leading to indentation of the breast contour, breast lumps that enlarge, persistent breast lumps, and breast lumps associated with unilateral spontaneous nipple discharge, are highly associated with a subsequent diagnosis of breast cancer (Mahoney *et al.*, 1982; Giess *et al.*, 1998; Dolan *et al.*, 2010; Chen *et al.*, 2011). Unilateral spontaneous bloody discharge without a readily palpable breast lump may be associated with breast cancer (Montroni *et al.*, 2010; Chen *et al.*, 2011).

Whereas referral of women with small lumps may lead to the diagnosis of "early breast cancer", the presence of a lump in the axilla, extensive nipple or skin retraction or tethering, lumps fixed to the skin or chest wall and skin changes such as thickened skin, peau d'orange, or ulceration may be associated with advanced breast cancer (Smith *et al.*, 1976; Mahoney *et al.*, 1982; Halder *et al* 2001).

Women with early breast cancer may develop symptoms such as a change in the consistency of one area in a breast (compared to the other breast), skin tethering or dimpling, or a change in the shape of the breast without necessarily presenting with a discrete lump (Bassett, 1985).

Pain in the breast without palpable breast lumps or other symptoms is unlikely to be associated with a diagnosis of breast cancer (Masroor *et al.*, 2009; Smith *et al.*, 2004; Clegg-Lamptey *et al.*, 2007; Obene-Yaboah *et al.*, 2008).

Recommendations (See Figure 2)

Based on the GRADE evaluation, the GDG clinical considerations, and the high value placed by all GDG members in detecting **breast cancer** in earlier stages, the following are strong recommendations for referral of women with possible breast cancer:

- Women who report any breast symptoms at PHC should undergo physical examination of both breasts, both axillae, and the neck prior to referral.

- Women with a palpable breast lump, unilateral spontaneous nipple discharge (particularly bloody discharge), or any change in the shape or consistency of the breast, whether or not associated with other symptoms or risk factors, should be referred to a facility where diagnosis, staging, and treatment of breast cancer can be efficiently carried out as indicated below:

  - Women **aged 30 years and above** with a breast lump, unilateral spontaneous nipple discharge (particularly bloody discharge), skin changes such as eczematous changes in or around the nipple or areola, skin tethering, and skin or nipple retraction should be referred for further investigations to rule out breast cancer.

  - Women **under the age of 30 years** with a breast lump should only be referred for further investigations if the lump enlarges or has other features associated with cancer (such as fixed or hardness or the presence of skin changes) or in whom there are other reasons for concern, such as a family history of breast cancer, former breast cancer or prior therapeutic chest irradiation.

Figure 2: Assessment and referral of women with suspected breast cancer at primary health care

Women who present the following persistent and unexplained signs and symptoms should seek consultation at a PHC:

a) Breast lump, or any change in the shape or consistency of the breast

b) Breast lump that enlarges and/or is fixed and hard

c) Other breast problems (i.e. eczematous skin changes, nipple retraction, peau d'orange, ulceration, unilateral nipple discharge – particularly bloody discharge –, lump in the axilla) with or without palpable lump

ASSESS LIKELIHOOD FOR BREAST CANCER

- Assess signs and symptoms (i.e. history, intensity, duration, progression)
- Identify relevant breast cancer risk factors (such as age, family history, previous history of breast cancer, chest irradiation)
- Clinical examination of both breasts, axillae and neck
- Differential diagnosis: benign breast diseases (e.g. fibroadenoma, fibroadenosis, mastitis, abscess, etc.)

Women < 30 years old | **Women 30 years old and above**

Presenting with a)

Presenting with:
a) + relevant risk factors, or
b) or c)

Presenting with:
a) b) or c)

Invite for follow-up visit after menstrual period

Follow-up visit: if b) or c)

Refer immediately to next level

Note:
Referral of women with small breast lumps may lead to diagnosis of "early breast cancer"

- Women with any other symptom highly indicative of advanced breast cancer (such as a large lump in the breast, skin ulceration, axillary swelling, palpable axillary nodes, swelling in the neck, severe back pain) should also be referred to a specialized centre for diagnosis and appropriate care.

- Women found with no abnormalities upon physical examination should be taught breast awareness. This comprises educating them on breast cancer signs and symptoms, encouraging them to be aware of their normal breast and of any changes by periodic self-palpation, as well as empowering them to seek care promptly in case of any future breast abnormalities.

In making a recommendation to the patient for further investigation in specialized services, it should generally be emphasized that the likeliest possibility is that the lump is not a cancer. Benign breast diseases such as fibroadenoma, fibroadenosis, mastitis, abscess, benign cystic disease of the breast, and other rare diseases may also present with a lump in the breast. However, it is important to undergo further investigation because in the event cancer is diagnosed, treatment outcome is much better when the cancer is detected early and treated properly.

Referral of women with suspected cervical cancer

What are the signs and symptoms in women presenting at PHC that could lead to referral of suspected cervical cancer to specialized services?

Post-coital bleeding

GRADE evaluation:

One community study gave a relative risk for invasive carcinoma of 6.3 for bleeding on sexual intercourse (post-coital bleeding) compared to women without the symptom. A follow-up study of the same cohort of women found that those with post-coital bleeding and a negative screen had up to a 15-fold risk of late invasive cervical cancer compared to those without bleeding symptoms (but 93% of women who developed cervical cancer had not experienced post-coital bleeding). The quality of evidence was graded as very low (see GRADE Table 2 in Annex I).

GDG considerations:

Abnormal vaginal bleeding (bleeding that occurs after coitus, between menstrual periods, or after menopause) or persistent,[6] foul-smelling discharge that may or may not be tinged with blood are the cardinal signs of cervical cancer (Shapley *et al.*, 2006; Sarkar *et al.*, 2010; Ikechebelu *et al.*, 2010). These signs may be associated with early stages of invasive cervical cancer, particularly in women above the age of 30 years. However, abnormal vaginal bleeding in sexually active women is more frequently caused by abortion (in pre-menopausal women) and benign conditions such as cervical infections (including gonorrhoea and chlamydiae) ulceration due to cervical inflammatory disease, uterine polyps, and dysfunctional uterine bleeding due to hormonal imbalance. Similarly, persistent, foul smelling discharge may be associated with other conditions such as bacterial vaginosis, trichomoniasis, and vaginal candidiasis. Moreover, abnormal vaginal bleeding may sometimes be caused by other malignant conditions such as endometrial or vaginal cancer.

Some women with cervical cancer may experience pain during vaginal intercourse The association of a palpable abdominal mass with persistent low back or abdominal pain is usually associated with advanced cervical cancer and should raise suspicion of this possibility.

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6   That is, discharge that does not respond to syndromic treatment.

Recommendations (See Figure 3)

Based on the GRADE evaluation, the GDG clinical considerations, and the high value placed by all GDG members in detecting invasive cervical cancer in earlier stages, the following are strong recommendations for referral of women with possible cervical cancer:

■ Women who report any gynaecological sign or symptom suspicious of early cervical cancer (such as abnormal vaginal bleeding,[7] or persistent, foul-smelling discharge, or pain during vaginal intercourse) should, where possible, undergo a speculum examination. The following important issues should be taken into consideration:

  ■ In women with abnormal vaginal bleeding, with persistent, foul-smelling discharge, or experiencing pain during vaginal intercourse, the **presence of a cervical growth or ulceration** should prompt immediate referral for diagnostic confirmation and management without manipulation because of the significant risk of bleeding, which may be difficult to control.

  ■ Women with abnormal vaginal bleeding, with persistent, foul-smelling discharge, or experiencing pain during vaginal intercourse, **without clinically detected cervical growth or ulceration**, are likely to have a non-malignant condition, particularly if they are under 30 years of age. These women should be treated as appropriate[8] and be referred to a specialist to rule out cervical cancer only if the condition persists or has worsened at the time of a follow-up visit.

■ Women with any signs or symptoms associated with advanced cervical cancer (severe abdominal pain, abdominal distension, severe back pain, neck swelling, or symptoms of urethral and rectal fistula) should also be referred to a specialized centre for confirmation diagnosis and appropriate care.

■ In making a recommendation for further investigation, it should be emphasized that the likeliest possibility is that vaginal bleeding or foul-smelling discharge with or without clinically detected cervical growth or ulceration are not caused by a cancer. However, it is important to undergo further investigation because, in the event that cancer is diagnosed, the treatment outcome is much better when the cancer is detected early and treated properly. This is particularly relevant in women 30 years and above who are at higher risk of developing cervical cancer.

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7   Abnormal vaginal bleeding includes occurrences after coitus, between menstrual periods, or after menopause.

8   For further information consult the following *WHO guidelines: WHO Guidelines for the Management of Sexually Transmitted Infections (WHO 2003) and Managing Complications in Pregnancy and Childbirth: a guide for midwives and doctors* (WHO 2000, reprinted 2007).

Figure 3: Assessment and referral of women with suspected cervical cancer at primary health care

Women who present the following persistent and unexplained signs and symptoms should seek consultation at a PHC:
a) Abnormal vaginal bleeding (i.e. after coitus, between menstrual periods, post menopause)
b) Foul-smelling discharge
c) Pain during vaginal intercourse
d) Any of the above associated with palpable abdominal mass with persistent low back or abdominal pain

ASSESS LIKELIHOOD FOR CERVICAL CANCER
- Assess signs and symptoms (i.e. history, intensity, duration, progression)
- Identify relevant risk factors: age (30 years old and above)
- Speculum examination
- Differential diagnosis: abortion in pre-menopausal women, infections (e.g. Chlamydiae, gonococcal, etc.), genital ulcers, cervical inflammation, uterine polyps, dysfunctional uterus hemorrhage, endometrial or vaginal cancer

Women presenting with a) b) or c)

Women presenting with d)

Without clinically detected cervical growth or ulceration

With clinical detected cervical growth or ulceration

Follow obstetric and gynecological guidelines as appropriate

Refer if condition is not manageable at PHC, persists or worsens

Refer immediately to next level

Note: Referral of women with a) b) or c) may lead to a diagnosis of "early invasive cervical cancer", particularly in women **30 years old and above**.

See CD for:

■ Acknowledgements   53

■ Web-based resources

■ Annex 1 Evidence assessment and Grade tables

■ Annex 2 Evidence on risk factors,

■ References

■ List of contributors

See CD for:

■ Acknowledgements

Management of asthma and chronic obstructive pulmonary disease in primary health care in low-resource settings

Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
AQoL	asthma-specific quality of life
CFC	chlorofluorocarbon
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
CRQ	Chronic Respiratory Questionnaire
FEV1	forced expiratory volume in 1 second
FVC	forced expiratory vital capacity
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFA	hydrofluoroalkane
HIV	human immunodeficiency virus
HQ	headquarters
HRQol	health-related quality of life
IUATLD	International Union Against Tuberculosis and Lung Disease
kg	kilogram
LMIC	low- and middle-income country
MD	mean dose
MDI	metered-dose inhaler
MeSH	Medical Subject Headings
mg	milligram
ml	milliliter
NCD	noncommunicable disease
OR	odds ratio
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PICOT	population/intervention/comparator/outcome/time
prn	pro re nata (as needed)
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SGRQ	St George's Respiratory Questionnaire
SMD	standardized mean difference
ug	microgram
WHO	World Health Organization

Executive summary

Chronic respiratory diseases (CRDs), particularly bronchial asthma and chronic obstructive pulmonary disease (COPD), are major public health problems accounting for a considerable share of the disease burden in low- and middle-income countries (LMICs). In 2004, 6.8% of deaths in women and 6.9% in men in LMICs were caused by CRDs, according to the *WHO Global burden of disease report: update 2004.*

Prevention and control of CRDs need to be addressed through a public health approach, including the implementation of key interventions at a primary health care level. It is particularly important to give due consideration to the limited resources available in LMICs where the use of essential medicines and equipment and the availability of health workers need to be prioritized.

According to the World Health Organization (WHO) 2008–2013 Action Plan for the Global Strategy for Prevention and Control of Noncommunicable diseases (WHO Global NCD Action Plan), endorsed by the World Health Assembly in 2008, WHO is called upon to provide technical guidance to countries for the integration of cost-effective interventions against major NCDs in their health systems. This guideline is a tool that provides such assistance.

The care offered at present to patients with CRDs is not always based on evidence or best practice and this is the first time WHO has produced a guideline for the management of asthma and COPD through a primary care approach in resource-limited settings. This guideline is designed for easy access and implementation in busy community clinics and small hospitals and is intended to complement other evidence-based guidelines such as the International Union Against Tuberculosis and Lung Disease (IUATLD) and the Global Initiative for Asthma (GINA) guidelines. These guidelines should be referred to if more information is required; for example, on classification of disease severity.

The main purpose of this guideline is, therefore, to provide evidence-based recommendations on management of asthma and COPD in primary health care in low-resource settings. The target users are physicians and health workers. The main objectives are to reduce avoidable death and morbidity related to asthma and COPD and to improve health outcomes in resource-limited settings where management facilities are limited in terms of availability of diagnostic facilities and medicines.

The guideline is concerned with the management of asthma and COPD by:

■ focusing at a primary health care level in low-resource settings;

■ assisting the users who will be physicians and health workers in primary care, and staff in government health departments concerned with procuring drugs[1];

■ safeguarding affordability by organizing drug treatment around four major groups of medicines on the WHO Essential Medicines List (salbutamol, beclometasone, prednisolone, antibiotics) – other drugs are mentioned only if they have been shown to be helpful and if they are sometimes available and used in resource-poor countries, e.g. oral theophylline;

■ assuring that all complicated or severe cases are referred to the next level of care.

The strength of the recommendations for the management of asthma and COPD that are developed, summarized and presented in this guideline reflects the degree of confidence that the desirable effects of adherence to the recommendations outweigh the undesirable effects. As described in the guideline, the following factors were considered during the recommendation making process: (i) quality of evidence; (ii) uncertainty of balance between desirable and undesirable effects; (iii) variability in values and preferences of outcomes by different individuals; and (iv) cost effectiveness.

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1   See integrated protocols and other tools for Best Buys and WHO Package of Essential Noncommunicable Disease in CD, to facilitate guideline implementation in primary care)

Recommendations

* Strength of recommendation/Quality of evidence

Management of stable asthma

REC 1: In order to determine the best management approach, asthma control should be assessed using severity and frequency of symptoms. (Particularly nocturnal symptoms, exercise induced wheezing, the use of beta agonists and absence from work/school due to symptoms, the frequency of exacerbations and peak expiratory flow (PEF) if available.) *** (***Strong recommendation, low quality evidence***) Annex 4.1; 4.2**

REC 2: Inhaled corticosteroids (beclometasone) should be given to all patients with chronic persistent asthma. If their use needs to be prioritized in resource-constrained settings, the highest priority group should be those with life-threatening attacks and attacks requiring hospital admission where the use of a regular inhaled steroid is likely to save money by reducing hospital admissions. Patients with frequent exacerbations are also a high priority group, as are those with persistent troublesome symptoms, those using high doses of beta agonists and those losing time from work or school.

Numerous studies have demonstrated that inhaled steroids reduce asthma exacerbations and improve lung function, although they vary in terms of dosage used, type of steroid and mode of delivery, including the use of a spacer. Low doses (e.g. beclometasone 100ug once or twice daily for children and 100ug or 200ug twice daily for adults) are adequate for most patients with mild or moderate asthma; patients with more severe asthma require higher doses.

The lowest dose of beclometasone that controls symptoms should be determined for maintenance treatment. Any deterioration in symptom control should be treated with an increase in dose. A spacer should be used with a metered-dose inhaler (MDI) to reduce candidiasis and increase drug deposition in the lung.

Ensuring that low-cost, good quality generic preparations of inhaled beclometasone are readily available for all patients with persistent asthma is the highest priority.
* (*Strong recommendation, moderate quality evidence***) Annex 4.3; 4.4**

REC 3: A stepwise approach to treatment is recommended:

- Step 1. Inhaled beta agonist (salbutamol) as required (prn)
- Step 2. Continue inhaled salbutamol prn and add inhaled beclometasone 100ug or 200ug twice daily, or 100ug once or twice daily in children

- Step 3. Continue inhaled salbutamol prn and increase the dose of beclometasone to 200ug to 400ug twice daily

- Step 4. Add low-dose oral theophylline (assuming that long-acting beta agonists are not available), or increase dose of inhaled beclometasone

- Step 5. Add oral prednisolone in the lowest dose possible to control symptoms

At each point it is important to check patients' adherence to their medications and that their inhaler technique is correct. For patients requiring regular prednisolone referral to a specialised centre should be considered.
* Annex 7

Management of exacerbation of asthma

REC 1: Oral prednisolone should be given for all acute exacerbations of asthma. For adults, a dose of 30–40mg daily is appropriate, while for children (<16 years) a dose of 1mg per kg daily has fewer adverse effects on behaviour than 2mg per kg, so a dose of 1mg per kg (up to 30mg daily) is recommended. Patients should have easy access to oral corticosteroids for exacerbations. In children, prednisolone tablets can be crushed and given with sugar. The usual duration of treatment is three days for children and five days for adults though it may need to be extended if the patient has not recovered fully.
* (*Strong recommendation, low-quality evidence***) Annex 4.6**

REC 2: Inhaled salbutamol: higher doses of inhaled salbutamol should be given to all patients with acute severe exacerbations; salbutamol may be given by nebulizers or spacers (commercial or homemade). The evidence suggests no important advantages of nebulizers over spacers in children over the age of 2 (or adults) although these studies did not include patients with life-threatening asthma. Other considerations may be relevant in making the choice between nebulizers and spacers such as the availability of nebulizers, the need to prevent cross-infection and whether the patient will use a spacer at home. Steps must be taken to keep nebulizers and spacers clean (sterile) and to prevent transmission of infections.

Following treatment with salbutamol, patients should have repeat clinical assessments at intervals (e.g. 15–20 minute intervals) to ensure that they are responding to treatment. Failure to respond requires further doses or more intensive treatment.

Once the patients have recovered, their usual maintenance treatment should be reviewed and altered if indicated to prevent recurrent exacerbations.
* (*Strong recommendation, low-quality evidence***) Annex 4.7; 4.8; 4.15**

REC 3: Oxygen: if available, oxygen should be administered to patients with acute severe asthma. This is in keeping with normal practice in high-resource settings where the decision to use oxygen is based on low oxygen saturation readings.
* (*Strong recommendation, very low-quality evidence***)**

REC 4: Second-line drugs: if patients do not respond to salbutamol and prednisolone, then second-line drugs may need to be considered. If a nebulizer and ipratropium bromide are available and a second-line treatment is required, nebulized ipratropium bromide is recommended for children with acute asthma.
* (*Weak recommendation, very low-quality evidence***)**

REC 5: Intravenous magnesium: at present, there is insufficient evidence to recommend intravenous magnesium as a routine second-line drug.
* (*Weak recommendation, very low-quality evidence***)**

REC 6: Intravenous salbutamol: on the basis of the balance between benefits and risks, intravenous salbutamol is NOT recommended for use as a second-line drug.
* (*Strong recommendation, very low-quality evidence***)**

REC 7: Intravenous aminophylline: on the basis of the balance between benefits and risks, intravenous aminophylline is NOT recommended for routine use as a second-line drug. When taken in addition to beta agonists and steroids there is no significant benefit for adults and only marginal benefit for children. There is evidence of adverse effects for children and adults. The risks are seen as outweighing the benefits in settings where monitoring is not feasible.
* (*Weak recommendation, very low-quality evidence***)**

Management of stable COPD

REC 1: When given as required short-acting beta-agonists are effective in improving symptoms in patients with stable COPD. Patients should be prescribed beta agonists as required. There are no data from which to assess the optimum frequency of administration, or the effect of regular administration. Inhaled beta agonists are recommended rather than oral preparations because oral preparations have more pronounced undesirable effects that may be of particular relevance in view of common co-morbidities with COPD, e.g. arrhythmias in patients with coronary heart disease.
* (*Weak recommendation, very low-quality evidence***) Annex 4.11; 4.12**

REC 2: Theophylline: as it is unlikely that blood levels can be monitored in resource-constrained settings, only low doses of theophylline

are recommended. Patients should be advised to stop treatment and consult a doctor if adverse effects are experienced.
* (*Weak recommendation, very low-quality evidence***) Annex 4.14**

REC 3: Oral corticosteroids (prednisolone) are ineffective in stable COPD except possibly in high doses when there are important side effects. On the basis of the balance between benefits and risks, oral steroids are NOT recommended for use in stable COPD.
* (*Strong recommendation, very low-quality evidence***) Annex 4.13**

REC 4: Inhaled steroids (beclometasone): when given in high doses there may be a small benefit from inhaled steroids; however, high doses are expensive for resource-poor countries and high doses have more adverse effects, including pneumonia. The risks are unknown in areas where the prevalence of HIV and tuberculosis are high. Since the benefit is modest, the risk/benefit ratio is much higher than it is for asthma. The use of inhaled steroids for patients with stable COPD therefore cannot be justified. NOT recommended.
* (*Strong recommendation, very low-quality evidence***)**

REC 5: Ipratropium bromide: when compared to regular short-acting beta agonists, short-term inhaled ipratropium bromide has small benefits with regard to reducing symptoms and improving lung function. Currently, ipratropium bromide preparations are more expensive than beta agonists and there are no data to assess risk versus benefits of regular use over longer periods to recommend long-term regular use of ipratropium bromide. NOT recommended.
* (*Weak recommendation, very low-quality evidence***) Annex 4.12**

Management of exacerbation of COPD

REC 1: **Antibiotics** should be given for COPD exacerbations.
* (*Strong recommendation, very low-quality evidence*) **Annex 4.10**

REC 2: Oral steroids: a short course of prednisolone is recommended for acute severe exacerbations of COPD (e.g. prednisolone 30–40mg for about seven days).
* (*Strong recommendation, very low-quality evidence*) **Annex 4.14**

REC 3: Inhaled beta agonists: higher doses of inhaled salbutamol should be administered via a nebulizer or spacer.
* (*Strong recommendation, very low-quality evidence*) **Annex 4.12**

REC 4: Oxygen: if available, oxygen should be administered by a device that controls concentration to 24%–28%.
* (*Strong recommendation, very low-quality evidence*)

REC 5: Intravenous aminophylline: based on the available evidence, intravenous aminophylline is NOT recommended for routine use in acute exacerbations of COPD. Although there are data from only four studies, these show little evidence of benefit; any beneficial effect is likely to be small and is likely to be outweighed by potential adverse effects.
* (*Strong recommendation, very low-quality evidence*)

The summaries of the considerations of benefits/risks, values, cost and feasibility for the recommendations listed in the following table were discussed by the guideline expert panel based on the experience of its members, consideration of the systematic reviews, moderated discussion and consensus.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
Management of stable asthma	
REC 1	Standard diagnostic recommendations to assess asthma control should be used in accordance with standard clinical practices, as agreed by the guideline expert panel members.
REC 2	**Benefits:** Highly effective treatment for control of stable asthma as well as significant reduction of exacerbations and improvement of lung function. **Risks:** Risks of side effects are minimal since only the lowest dose that controls symptoms is recommended for maintenance treatment. A spacer should be used with an MDI to reduce candidiasis with beclometasone and increase drug deposition in the lung. **Values and acceptability:** Numerous studies have demonstrated that inhaled steroids reduce asthma exacerbations and improve lung function, although they vary in terms of dosage used, type of steroid and mode of delivery, including the use of a spacer. **Cost:** The regular use of inhaled steroids is likely to save money by reducing hospital admissions of patients with life-threatening attacks and frequent exacerbations. Low-cost, good quality generic preparations of inhaled steroids are recommended. **Feasibility:** Particularly recommended in resource-constrained settings where access to medical care is often restricted.
REC 3	A stepwise approach is a commonly accepted way of managing asthma patients and basically comprises all the other treatment recommendations, as agreed by the guideline expert panel members.
Management of exacerbation of asthma	
REC 1	**Benefits/risks:** Benefits far outweigh the risks. For all acute exacerbations of asthma, short-term courses of oral steroids in the recommended doses are effective and carry minimal risk of side effects, e.g. weight gain, fluid retention, high blood pressure, elevated blood sugar. **Values and acceptability:** The efficiency in acute exacerbations of asthma is demonstrated in numerous studies. In the recommended doses, a significant benefit is derived with little risk of side effects. **Cost:** Affordable for resource-constrained settings. **Feasibility:** There should be easy access to oral corticosteroids for patients with exacerbations of asthma.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
REC 2	**Benefits/risks:** Effective for improving lung function in patients with acute exacerbations of asthma. For short-term administration of high doses, benefits outweigh the risk of potential side effects. Generally, the evidence suggests no important advantages of nebulizers over spacers. **Values and acceptability:** Based on the severity of asthma exacerbations, prompt treatment can be vital. Following treatment with salbutamol, the patient should have repeated clinical assessments at intervals (e.g. 15–20 minute intervals) to ensure that they are responding to treatment. Failure to respond requires further doses or more intensive treatment. **Cost:** There are no data available directly assessing the cost effectiveness, although, the cost is lower where good quality generic preparations are available. **Feasibility:** Higher doses of inhaled beta agonists should be given to all patients with acute severe exacerbations where available.
REC 3	**Benefits/risks:** In the absence of evidence from randomized controlled trials (RCTs) in asthma, the recommendation is based on observational evidence and strong consensus belief that oxygen is beneficial. **Values and acceptability:** If oxygen is available, it should be administered to all patients with acute severe asthma in keeping with normal practice in high-resource settings where the decision to use oxygen is based on low oxygen saturation readings (pulse oximetry). **Cost:** Short-term use in exacerbations as recommended should be affordable.
REC 4	If a nebulizer and ipratropium bromide are available and a second-line treatment is required, adding ipratropium bromide can be recommended for children with acute asthma but ONLY as a second-line treatment. Side effects are rare; paradoxical bronchoconstriction is a recognised though rare problem. **Cost:** There are no data available directly assessing the cost effectiveness, although the cost is lower where good quality generic preparations are available.
REC 5	**Negative recommendation.** At present, there is insufficient evidence to recommend intravenous magnesium as a routine second-line drug and is NOT recommended. However, if it is available, it may be worth trying if the patient continues to deteriorate despite other recommended treatment.
REC 6	**Negative recommendation.** On the basis of the balance between benefits and risks, intravenous salbutamol is NOT recommended for use as a second-line drug.
REC 7	**Negative recommendation.** On the basis of the balance between benefits and risks and because the risks outweigh the benefits in settings where monitoring of blood drug levels is not feasible, intravenous aminophylline is NOT recommended for routine use as a second-line drug.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
	Management of stable COPD
REC 1	**Benefits/risks:** When given as required beta agonists are effective in improving symptoms in patients with COPD. The effect of regular administration is unknown. **Values and acceptability:** Inhaled beta agonists are recommended rather than oral preparations because oral preparations have more pronounced undesirable effects that may be of particular relevance in view of common co-morbidities with COPD, e.g. arrhythmias in patients with coronary heart disease. **Cost:** There are no data available directly assessing the cost effectiveness, although the cost is lower where good quality generic preparations are available. It is feasible with an MDI.
REC 2	**Benefits/risks:** Theophylline can cause serious adverse effects, particularly if therapeutic blood concentrations are exceeded. Only low-dose slow-release theophylline can be recommended as being relatively safe and providing some efficacy. **Values and acceptability:** Low-dose, slow-release oral theophylline can be effective and well tolerated in the long-term treatment of stable COPD. **Cost:** No data available. **Feasibility:** As it is unlikely that blood levels can be monitored in resource-constrained settings, only low doses of theophylline are recommended. Patients should be advised to stop treatment and consult a doctor if adverse effects are experienced.
REC 3	**Negative recommendation.** Oral corticosteroids (prednisolone) are ineffective in stable COPD except possibly in high doses when there are important side effects. On the basis of the balance between benefits and risks, oral steroids are NOT recommended for use in stable COPD.
REC 4	**Negative recommendation.** When given in high doses, there may be a small benefit from inhaled steroids. However, high doses have more adverse effects and are more expensive, while any benefit is small. Their use for patients with stable COPD cannot be justified when resources are limited.
REC 5	**Negative recommendation.** Compared to regular short-acting beta agonists, short-term inhaled ipratropium bromide has small benefits with regard to reducing symptoms and improving lung function. Currently, ipratropium bromide preparations are more expensive than beta agonists and there are no data to assess risk versus benefits of regular use over longer periods to recommend long-term regular use of ipratropium bromide, thus they are NOT recommended.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
Management of exacerbation of COPD	
REC 1	**Benefits/risks:** Since benefits significantly outweigh side effects, antibiotics should be given for all COPD exacerbations with purulent sputum and signs of systemic infection. **Values and acceptability:** Antibiotics are commonly prescribed empirically. Which antibiotic should be prescribed needs to be decided locally according to likely organisms, cost and availability. **Cost:** The cost depends on the antibiotic used.
REC 2	**Benefits/risks:** Benefits usually outweigh the risks. Short-term courses of oral steroids in the doses recommended are of benefit for acute exacerbations of COPD and usually have few side effects. **Values and acceptability:** A short course of oral steroids is beneficial and with the doses recommended is associated with minimum risk. However, it is important to weigh potential benefits against side effects for each patient. **Cost:** Affordable for resource-constrained settings. **Feasibility:** There should be easy access for patients with exacerbations of COPD.
REC 3	**Benefits/risks:** Effective for improving lung function in patients with acute exacerbations of COPD. For short-term administration for exacerbations, the benefits of high doses outweigh the risk of potential side effects. The evidence suggests no important advantages of nebulizers over spacers. **Cost:** There are no data available directly assessing the cost effectiveness, although the cost is lower where good quality generic preparations are available. **Feasibility:** Higher doses of inhaled beta agonists should be given to all patients with acute severe exacerbations of COPD where available. Administration either by MDI and spacer or by nebulization is acceptable.
REC 4	**Benefits/risks:** This recommendation is based on observational evidence and strong consensus belief that oxygen is beneficial. High concentrations of supplemental oxygen can lead to the accumulation of carbon dioxide and respiratory acidosis for some people with severe COPD. It is very important, therefore, that when oxygen is administered it is given in a low concentration (24%–28%) using a controlled oxygen delivery device. Patients clearly should not smoke if using or close to an oxygen supply. **Values and acceptability:** If oxygen is available, it should be administered for exacerbations of COPD, as long as a low concentration can be given as prescribed. **Cost:** Short-term use in exacerbations as recommended should be affordable.

Recommendation	Benefits/risks; values and acceptability; cost; feasibility
REC 5	**Negative recommendation.** Based on the available evidence, intravenous aminophylline is NOT recommended for routine use in acute exacerbations of COPD. Although there are data from only four studies, they show little evidence of benefit; thus any beneficial effect is likely to be small and the risks outweigh benefits.

Methodology used to prepare the guideline

The WHO Guideline for Management of Asthma and COPD through a Primary Care Approach in Resource-constrained Settings was prepared according to the WHO Handbook for Guideline Development. The scope in the format of PICOT questions was defined by WHO and circulated to the guideline expert panel members for comments in advance of the guideline expert panel meeting (Annex 3).

The Cochrane Airways Group was consulted to design the search strategy for the finalized scoping questions. A methodologist was contracted to assess the quality of evidence using the Assessment of Multiple Systematic Reviews (AMSTAR) tool and to prepare evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The AMSTAR instrument is a validated tool for critically appraising the methodological quality of systematic reviews. It consists of an 11-item questionnaire with each item receiving a score of 1 if the specific criterion was met or a score of 0 if the information was not reported or was unclear or the criterion was not applicable. After applying AMSTAR, the review that scored the highest was selected. Systematic reviews were assessed rather than single studies.

The evidence was assessed according to the GRADE methodology. In this system evidence is classified as high, moderate, low or very low and is defined as follows:

- High: further research is very unlikely to change our confidence in the estimate of effect.

- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

- Very low: any estimate of effect is very uncertain.

Factors that were considered in classifying the evidence were: (i) the study design and rigour of its execution; (ii) the consistency of results and how well the evidence can be directly applied to patients; (iii) interventions; (iv) outcomes; and (v) comparator. Other important factors were whether the data were sparse or imprecise and whether there was potential for reporting bias.

The recommendations were drafted according to the GRADE methodology for assessing the quality of evidence and strength of

recommendations. The guideline expert panel, comprising clinical experts and scientists in the area of CRDs, guideline methodology, research, pharmacology and policy-making, was convened on 20–21 December 2010 at WHO headquarters in Geneva (see Annex 1 for the list of participants). The meeting was preceded by several teleconference discussions and e-mail consultations. The priority questions and scope of the guideline were discussed and finalized based on the comments provided by the expert panel members during these discussions preceding the meeting.

The guideline expert panel members were involved in the following:

■ advising on the priority of questions and scope of the guideline;

■ advising on the choice of important outcomes for decision-making;

■ commenting on the evidence used to inform the guideline;

■ advising on the interpretation of the evidence, with explicit consideration of the overall balance of risks and benefits of each particular intervention for asthma and COPD patients;

■ formulating recommendations, taking into account the scope of the guideline, its target audience and resource-constrained settings.

At the guideline expert panel meeting, the members were asked to identify critical clinical outcomes for the purposes of making the recommendations. The expert panel reviewed the available evidence summaries and made recommendations. All recommendations were based on consensus and in accordance with the assessed evidence.

All declarations of interests of the guideline expert panel members were reviewed before the guideline expert panel meeting (Annex 2). None of the members declared any potential conflict of interests relevant to the discussion and recommendations, either personal or institutional. The GRADE tables (Annex 4) were prepared by the members of the guideline expert panel and the methodologist.

Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs and values, and preferences. Recommendations were classified as strong or weak, as recommended in the GRADE methodology.

For each recommendation, the final agreement was based on group consensus by the guideline expert panel members using a combination of the following factors:

■ evidence balanced for benefits/risks of the intervention;

■ costs, values and feasibility of each particular intervention in resource-constrained settings;

■ quality of evidence itself (high, moderate, low, very low);

■ preferences of the group based on clinical experience of the expert panel members.

Each recommendation was formulated only when full consensus was reached among the expert panel members based on all of the above-mentioned points. As a result, each recommendation was classified either as strong or weak according to the GRADE methodology.

Strong recommendations can be interpreted as:

■ most individuals should receive the intervention;

■ most well-informed individuals would want the recommended course of action and only a small proportion would not;

■ could unequivocally be used for policy-making.

Weak recommendations can be interpreted as:

■ majority of well-informed individuals would want the suggested course of action, but an appreciable proportion would not;

■ widely varying values and preferences;

■ policy-making will require extensive debates and involvement of many stakeholders.

After the guideline expert panel meeting, the WHO Secretariat revised the draft guideline according to the recommendations from the guideline expert panel. Comments are reviewed by the WHO Secretariat and are being incorporated into the final version.

Identification of important outcomes

Summaries of the best available evidence were prepared to inform scoping questions. A list of potential outcomes to be considered by the guideline expert panel was developed both for asthma and COPD scoping questions. The panel members ranked these outcomes and were requested to identify any relevant critical outcomes not included on the list. The panel members were also asked to identify which outcomes they felt were critical, important but not critical, and not important.

The panel members were then asked to score the outcomes, using numbers corresponding to the GRADE importance of outcomes where 7–9 indicated the outcome was critical for a decision, 4–6 indicated it was important, and 1–3 indicated it was not important. Both the average scores for each outcome and the range of scores were considered. The individual scores were discussed and disagreements were resolved by consensus. Outcomes were included roughly in order of their relative importance in the GRADE tables (Annex 4).

Outcomes (asthma)	Outcomes (COPD)
Mortality	Mortality
Quality of life (QoL)	Quality of life (QoL)
Mechanical ventilation	Breathlessness
Cough	Cough
Wheeze	Wheeze
Dyspnoea	Sputum production
Distance walked	Distance walked
Drop-out	Drop-out
Adverse effects	Serious adverse events
PEFR	PEFR
FEV1	FEV1
FVC	FVC

Search strategy, selection criteria, data collection and judgement

The search strategy was to identify systematic reviews relevant to the scoping questions. Once systematic reviews were identified, searches were also conducted for RCTs in order to identify any additional trials not included in the reviews. Summaries of all identified systematic reviews were shared with members of the guideline expert panel before the December 2011 meeting.

For systematic reviews, an advanced search with Medical Subject Headings (MeSH) was conducted. The comprehensive search strategies designed by the Cochrane Airways Group based on approved PICOT questions are described in Annex 5 (in addition, the Cochrane Airways Group Asthma and COPD registers of RCTs were searched). The limits that were applied to the search included: published in the last 10 years; human being only; English language; systematic reviews.

As a result of the AMSTAR quality assessment of the found systematic reviews, nine systematic reviews for asthma and 14 systematic reviews for COPD PICOT questions were selected (Annex 6).

Evidence profiles based on the systematic reviews were created using the GRADE methodology (Annex 4). Using this approach, assessments of the quality of evidence for each important outcome took into account the study design, limitations of the studies, consistency of the evidence across studies, directness of the evidence with respect to the populations, interventions and settings, and the precision of the summary estimate of effect. If there were several relevant systematic reviews, the most recent one of the highest quality was used. The GRADE evidence profiles have been prepared with footnotes that explain the judgements that were made.

In the majority of cases, the quality of evidence for various outcomes ranged from *very low quality to moderate quality*. The primary reason for this is a lack of availability of evidence for the setting for which the recommendations were made, i.e. patient population from LMICs. In all cases, the quality of evidence was downgraded due to indirectness.

The draft recommendations have been sent for external peer review, which are analysed by WHO. The peer reviewers were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of the evidence base supporting the recommendations in the guideline. The document received positive appraisal; however, the comments of peer reviewers are then sent to the guideline expert panel members for their consideration and discussion. Based on the comments received, the WHO writing team will produce the final product. Comments and suggestions from peer reviewers will be addressed to the responsible officer for reply. Responses will be documented and made available upon request. The summary of peer reviewer comments from four independent experts with no conflict of interest is presented below; the full text is available upon request.

All peer reviewers were asked to submit a signed WHO Declaration of Interests form. Where interest was declared, legal advice was sought on whether the expert would be eligible for reviewing the document (Annex 2). The guideline development group is grateful to these reviewers for their contribution to the guideline.

Major comments of peer reviewers:

■ The guideline is focused mainly on treatment and does not address the issue of non-drug prevention such as tobacco or overweight control. Advice regarding these risk factors would be beneficial. (*Response: provided in the treatment flowcharts*.)

■ Advice on patient education and establishing a partnership "physician–patient" is important to mention. (*Response: provided in the treatment flowcharts*.)

■ Inhaled corticosteroids should include any other inhaled corticosteroids and not only beclometasone. (*Response: see summary decision-making tables*.)

■ Regarding stable COPD recommendations 1 and 4: the lack of studies for short-acting beta agonists >8 weeks appears to be the issue regarding the inability to recommend them regularly. It should be stated that there are no trials – it is not that the trials exist and demonstrate that there is no effect. The search is only up to 2002; in view of the importance of this and the probability of long-term benefits as described for trials >8 weeks, the guideline should make a clear interpretative comment about likely long-term benefits for

symptoms and lung function. (*Response: see summary decision-making tables*.)

It is planned initially to introduce the guideline (English printed version as well as an electronic version on the WHO web site) at regional and subregional workshops that will be organized with country support in close consultation with regional WHO representatives. Implementing partners will be invited to these workshops for wider incorporation. The indicators used to evaluate the impact of interventions will be discussed and selected at the workshops. WHO headquarters will provide technical support at the country level for local adaptation of the guideline. Staff from headquarters and regional and country offices will be familiarized with the guideline in order to assist the countries. It is expected that this guideline will be reviewed in 2016.

Annex 3. PICOT questions

Asthma

1. How does PEF monitoring compare to symptoms alone?

Population	children ≤16 years of age adults >16 years of age suffering from asthma
Indicator/ Intervention	PEF monitoring
Comparator	symptoms monitoring
Outcomes	FEV1 (level and rate of change) or PEF variability, symptoms improved, exacerbations, morbidity (hospitalization, emergency department visits, unscheduled doctor visits, lost days from work and school)

2. What evidence is there on PRN salbutamol versus placebo for mild asthma?

Population	children ≤16 years of age presenting with symptoms of asthma and on no treatment adults >16 years of age
Indicator/ Intervention	treatment with salbutamol as required
Comparator	no treatment or placebo
Outcomes	FEV1 (level and rate of change) or PEF variability, symptoms improved, exacerbations, morbidity (hospitalization, emergency department visits, unscheduled doctor visits, lost days from work and school)
Time	Short-term

3. What evidence is there on when to add beclometasone?

Population	children ≤16 years of age
	adults >16 years of age suffering from asthma treated with prn salbutamol alone or no treatment
Indicator/ Intervention	treatment with regular beclometasone at any dose twice daily
Comparator	regular placebo twice daily
Outcomes	FEV1 (level and rate of change) or PEF variability, symptoms improved, exacerbations, morbidity (hospitalization, emergency department visits, unscheduled doctor visits, lost days from work and school and relief medication use)
Time	more than 12 weeks, preferably at least six months

4. What evidence is there that oral prednisolone should be given in all cases of acute asthma?

Population	children ≤16 years of age
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/ Intervention	use of oral prednisolone
Comparator	oral prednisolone not used
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term

5. What evidence is there that supplementary oxygen should be given to all hypoxaemic patients with acute severe asthma?

Population	children ≤16 years of age adults >16 years of age suffering from acute severe asthma
Indicator/ Intervention	use of oxygen
Comparator	oxygen not used
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term

6. What is the evidence that salbutamol administered by nebulizer is more efficacious than salbutamol administered by spacer and MDI in acute asthma?

Population	children ≤16 years of age suffering from acute asthma exacerbation adults >16 years of age suffering from acute asthma exacerbation
Indicator/ Intervention	use of nebulizer
Comparator	use of commercial spacer and MDI delivery of salbutamol
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term

7. What is the evidence that salbutamol administered by commercial spacers is better than salbutamol administered by homemade spacers in acute asthma?

Population	children ≤16 years of age suffering from acute asthma exacerbation
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/ Intervention	use of commercial spacer and MDI delivery of salbutamol
Comparator	use of homemade spacer and MDI delivery of salbutamol
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department duration, lost days from work and school), mortality due to exacerbations
Time	short-term

8. What evidence is there that nebulized ipratropium bromide should be added to salbutamol for patients with acute severe or life-threatening asthma?

Population	children ≤16 years of age
	adults >16 years of age suffering from acute asthma exacerbation
Indicator/ Intervention	treatment with nebulized ipratropium bromide in addition to salbutamol
Comparator	nebulized salbutamol alone
Outcomes	FEV1 or PEF, symptoms (diaries), morbidity (hospitalization, emergency department visits, lost days from work and school), mortality due to exacerbations
Time	short- to long-term

COPD

1. What evidence is there regarding salbutamol as required for stable COPD treatment?

Population	adults >18 years of age with COPD
Indicator/ Intervention	treatment with salbutamol up to two puffs four times daily by MDI (with or without spacer)
Comparator	placebo
Outcomes	quality of life (SGRQ), exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

2. What evidence is there regarding ipratropium as required for stable COPD treatment?

Population	adults >18 years of age with COPD
Indicator/ Intervention	treatment with ipratropium up to two puffs four times daily by MDI (with or without spacer) in addition to inhaled salbutamol or alone
Comparator	placebo (when used in addition to inhaled salbutamol in both groups) or inhaled salbutamol alone (when compared to inhaled salbutamol)
Outcomes	quality of life, exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

3. What evidence is there on when to add theophylline?

Population	adults >18 years of age with COPD
Indicator/ Intervention	treatment with theophylline in addition to salbutamol or ipratropium
Comparator	salbutamol or ipratropium alone
Outcomes	quality of life (SGRQ), exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

4. What evidence is there on when to add beclometasone (inhaled corticosteroids) and in what dose?

Population	adults >18 years of age with COPD
Indicator/ Intervention	treatment with beclometasone by MDI (with or without spacer) in addition to inhaled salbutamol or ipratropium (but not long-acting beta2 agonists or tiotropium)
Comparator	salbutamol or ipratropium alone
Outcomes	quality of life (SGRQ), exacerbations (hospitalization, courses of oral corticosteroids, lost days from work)
Time	minimum of 12 weeks

5. What evidence is there on giving oral prednisolone in COPD exacerbations?

Population	adults >18 years of age COPD patients with acute exacerbation
Indicator/ Intervention	treatment with oral prednisolone for exacerbations
Comparator	placebo
Outcomes	hospitalization rate and duration, mortality due to exacerbations and complications, reconvalescence rate
Time	short- to medium-term

Annex VII
Summary of recommendations

Diagnosis and management of asthma

Stable asthma

Diagnosis

Asthma and COPD can both present with cough, difficult breathing, tight chest and/or wheezing. If uncertainty exists, the following features make a diagnosis of asthma more likely:

■ previous diagnosis of asthma;

■ symptoms since childhood or early adulthood;

■ history of hayfever, eczema;

■ intermittent symptoms with asymptomatic periods in between;

■ symptoms worse at night or early morning;

■ symptoms triggered by respiratory infection, exercise, weather changes or stress;

■ symptoms respond to salbutamol.

Measuring PEF before and 15 minutes after two puffs of salbutamol may also help. If the PEF improves by 20%, a diagnosis of asthma is very probable. However, in practice, most patients with asthma have a smaller response to salbutamol.

Assess asthma control

Asthma is considered to be well controlled if the patient has:

■ no more than two occasions a week when asthma symptoms occur and require a beta-agonist;

■ asthma symptoms on no more than two nights a month;

■ no or minimal limitation of daily activities;

■ no severe exacerbation (i.e. requiring oral steroids or admission to hospital) within a month;

■ a PEF, if available, above 80% predicted.

If any of these markers is exceeded, the patient is considered to have uncontrolled asthma.

Treatment

Treatment should be increased or decreased according to how well asthma is controlled and by using the stepwise approach described below. It is useful to start initially with a high step to achieve control and to show the patient that treatment can help, and then reduce the dose to the lowest dose to maintain control. Doses of beclometasone refer to those from an HFA fine dose inhaler; for equivalent doses from other inhalers, the dose may need to be doubled.

Stepwise approach

Step 1. Inhaled salbutamol prn

Step 2. Inhaled salbutamol prn plus low-dose inhaled beclometasone, starting with 100ug twice daily for adults and 100ug once or twice daily for children

Step 3. Same as step 2, but give higher doses of inhaled beclometasone, 200ug or 400ug twice daily

Step 4. Add low-dose oral theophylline to Step 3 treatment (assuming long-acting beta agonists and leukotriene antagonists are not available)

Step 5. Add oral prednisolone, but in the lowest dose possible to control symptoms (nearly always less than 10mg daily)

At each step, check the patient's adherence to treatment and observe their inhaler technique. A spacer normally should be used with MDIs since they increase drug deposition and reduce oral candidiasis with inhaled steroids.

Inhaled beclometasone should be available for all patients with persistent asthma, but if supplies are limited priority should be given to patients with life-threatening attacks and/or frequent exacerbations requiring hospitalization and those losing time from work or school.

Review asthma control

Patients with other than very mild asthma should have regular reviews every three or six months and more frequently when treatment has been changed or asthma is not well controlled. This should always include observation of inhaler technique.

Referral for specialist advice should, depending on facilities available, be considered:

- when asthma remains poorly controlled;
- when the diagnosis of asthma is uncertain;
- when regular oral prednisolone is required to maintain control.

Advice to patients and families

Regarding prevention:

■ avoid cigarette smoke and trigger factors for asthma, if known;

■ avoid dusty and smoke-filled rooms;

■ reduce dust as far as possible by using damp cloths to clean furniture, sprinkling the floor with water before sweeping, cleaning blades of fans regularly and minimizing soft toys in the sleeping area;

■ It may help to eliminate cockroaches from the house (when the patient is away) and shake and expose mattresses, pillows, blankets, etc. to sunlight.

Regarding treatment, ensure that the patient or parent:

■ knows what to do if asthma deteriorates;

■ understands the benefit from using inhalers rather than tablets, and why adding a spacer is helpful;

■ is aware that inhaled steroids take several days or even weeks to be fully effective.

Management of exacerbation of asthma

Assess severity

Assess the severity of asthma by analysing symptoms (ability to complete sentences), signs (e.g. heart rate) and PEF and oxygen saturation, if equipment is available.

Treatment

First-line treatment:

■ prednisolone 30–40mg for five days for adults and 1mg per kg for three days for children, or longer, if necessary, until they have recovered;

■ salbutamol in high doses by MDI and spacer (e.g. four puffs every 20 minutes for one hour) or by nebulizer;

■ oxygen, if available, and if oxygen saturation levels are low (below 90%).

Reassess at intervals depending on severity.

Second-line treatment – to be considered if the patient is not responding to first-line treatment:

■ Increase frequency of dosing via an MDI and spacer or by nebulizer, or give salbutamol by continuous nebulization at 5–10mg per hour, if appropriate nebulizer available;

- for children, nebulized ipratropium, if available, can be added to nebulized salbutamol.

Although the evidence for benefits from intravenous magnesium, intravenous salbutamol and intravenous aminophylline is poor, they may be worth trying, if available, when the patient has not responded to standard treatment and is at risk of dying from asthma.

Diagnosis and management of COPD

Stable COPD

Diagnosis

Both asthma and COPD can present with cough, difficult breathing, tight chest and/or wheezing.

If there is diagnostic uncertainty, the following features favour COPD:

- previous diagnosis of COPD;
- history of heavy smoking, i.e. >20 cigarettes per day for >15 years;
- history of heavy and prolonged exposure to burning fossil fuels in an enclosed space, or high exposure to dust in an occupational setting;
- symptoms started in middle age or later (usually after age 40);
- symptoms worsened slowly over a long period of time;
- long history of daily or frequent cough and sputum production often
- starting before shortness of breath;
- symptoms that are persistent with little day-to-day variation.

Measuring PEF before and 15 minutes after two puffs of salbutamol may also help. If the PEF improves by 20%, a diagnosis of asthma is very probable. A small response makes COPD more likely although a small response often occurs in asthma.

Assessing severity

Assess severity by symptoms (i.e. as moderate if breathless with normal activity and as severe if breathless at rest), and by PEF and oxygen saturation, if possible.

Treatment

- inhaled salbutamol, two puffs as required, up to four times daily;
- if symptoms are still troublesome, consider low-dose oral theophylline;
- if ipratropium inhalers are available, they can be used instead of, or added to, salbutamol, but they are more expensive.

Advice to patient and family

■ ensure they understand that smoking and indoor air pollution are the major risk factors for COPD. Patients with COPD must stop smoking and avoid dust and tobacco smoke;

■ keep the area where meals are cooked well ventilated by opening windows and doors;

■ cook with wood or carbon outside the house, if possible, or build an oven in the kitchen with a chimney that vents the smoke outside;

■ stop working in areas with occupational dust or high air pollution – using a mask may help, but it needs to have an appropriate design and provide adequate respiratory protection.

Exacerbation of COPD

Management

■ Antibiotics should be given for all exacerbations with evidence of infection.

■ For severe exacerbations, give oral prednisolone 30–40mg for around seven days.

■ Give high doses of inhaled salbutamol by nebulizer or MDI with spacer.

■ oxygen, if available, should be given by a mask that limits the concentration to 24% or 28%.

See CD for:

- GRADE tables
- Search strategies
- References
- Members of the Guideline Development Group

Diagnosis and management of type 2 diabetes in primary health care in low-resource settings

Executive Summary

The primary goal of the guideline is to improve the quality of care and the outcome in people with type 2 diabetes in low-resource settings. It recommends a set of basic interventions to integrate management of diabetes into primary health care. It will serve as basis for development of simple algorithms for use by health care staff in primary care in low-resource settings, to reduce the risk of acute and chronic complications of diabetes.

The guideline was developed by a group of external and WHO experts, following the WHO process of guideline development. GRADE methodology was used to assess the quality of evidence and decide the strength of the recommendations.

Recommendations

- Point of care devices can be used in diagnosing diabetes if laboratory services are not available.
  Quality of evidence: not graded
  Strength of recommendation: strong

- Advise overweight patients to reduce weight by reducing their food intake.
  Quality of evidence: very low
  Strength of recommendation: conditional

- Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
  Quality of evidence: moderate
  Strength of recommendation: conditional

- Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g walking).
  Quality of evidence: very low
  Strength of recommendation: conditional

- Metformin can be used as a first-line oral hypoglycaemic agent in patients with type 2 diabetes who are not controlled by diet only and who do not have renal insufficiency, liver disease or hypoxia.
  Quality of evidence: very low
  Strength of recommendation: strong

- Give sulfonylurea to patients who have contraindications to metformin or in whom metformin does not improve glycaemic control.
  Quality of evidence: very low
  Strength of recommendation: strong

- Give a statin to all patients with type 2 diabetes aged ≥ 40 years.
  Quality of evidence: moderate
  Strength of recommendation: conditional

- The target value for diastolic blood pressure in diabetic patients is ≤80mmHg.
  Quality of evidence: moderate
  Strength of recommendation: strong

- The target value for systolic blood pressure in diabetic patients is <130mmHg
  Quality of evidence: low
  Strength of recommendation: weak

- Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined.
  Quality of evidence: very low for thiazides, low for ACE inhibitors
  Strength of recommendation: strong

- Beta blockers are not recommended for initial management of hypertension in diabetic patients, but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.
  Quality of evidence: very low
  Strength of recommendation: strong

- Give patients health education of patients on foot hygiene, nail cutting, treatment of calluses, appropriate footwear.
  Quality of evidence: low
  Strength of recommendation: strong

- Educate health care workers on assessment of feet at risk of ulcers using simple methods (inspection, pin-prick sensation)
  Quality of evidence: low
  Strength of recommendation: strong

- Persons with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed and every two years thereafter, or as recommended by the ophthalmologist.
  Quality of evidence: low
  Strength of recommendation: conditional

- Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 should be given hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.
  Quality of evidence: strong
  Strength of recommendation: strong

- Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 mmol/L administer intravenously 20 to 50ml of 50% glucose (dextrose) over 1 to 3 minutes. If not available, substitute with any hypertonic glucose solution. Food should be provided as soon as the patient can ingest food safely.
  Quality of evidence: very low
  Strength of recommendation: strong

- If blood glucose ≥18 mmol (refer to hospital with i.v. drip 0.9% NaCl 1 litre in 2 hours, continue at 1 litre every 4 hours until hospital.
  Quality of evidence: very low
  Strength of recommendation: strong

These recommendations will be the basis for developing simple treatment algorithms for training primary care staff on integrated management of NCDs in low resource-settings.

Background

The implementation plan of the Global Strategy for Prevention and Control of Noncommunicable Diseases (NCDs) was endorsed by the World Health Assembly in May 2008. The objective 2 of this NCD Action Plan highlights the need to establish national policies and plans for NCD prevention and control (*1*). As one of the key components of this objective, WHO is called upon to "provide technical guidance to countries in integrating cost-effective interventions against major NCDs into their health systems". Furthermore, the Action Plan proposes that Member States "implement and monitor cost-effective approaches for the early detection of cancers, diabetes, hypertension and other cardiovascular risk factors" and "establish standards of health care for common conditions like CVD, cancers, diabetes and chronic respiratory diseases integrating when ever feasible their management into PHC".

Although there are several national and international guidelines on diabetes management, they are too complex for application in primary care in low-resource settings. The Global status report on noncommunicable diseases 2010 highlights the need for countries to integrate NCD prevention and management into primary health care even in low resource settings (2). WHO has identified an essential package of cost-effective interventions with high impact, feasible for application in resource-poor settings (3).

Objectives and target audience

The primary goal of the guideline is to improve the quality of care and the outcome in people with type 2 diabetes in low-resource settings. The guideline provides a basis for development of simple algorithms for management of diabetes with essential medicines and technology available in first-contact health services in low-resource settings. It recommends a set of basic interventions to integrate management of diabetes into primary health care. The recommendations are limited to patients with type 2 diabetes, as the more complex management of type 1 diabetes requires more specialized care.

The target users are health care professionals responsible for developing diabetes treatment protocols which will be used by health care staff in primary care units in low-resource settings.

A guideline development group was constituted, which included external experts and WHO staff (see CD).

Funding and declarations of interest

This work was funded by WHO funds.

Every member of the guideline development group and the peer reviewers (see CD for list of peer reviewers), completed a standard WHO declaration of interest forms (see CD).

Methodology and process

Scope of the guideline

The guideline development group used the GRADE methodology to formulate relevant questions on diabetes diagnosis and management in primary health care a low-resource context and identify important outcomes related to diabetes diagnosis and management (*4*). There were 12 questions to cover these domains:

■ Use of point-of-care devices (glucose meters) in diagnosing diabetes

■ Lifestyle management of diabetes

■ Use of medicines from the essential medicines list in managing hyperglycaemia

■ Use of medicines from the essential medicines list in reducing the risk of cardiovascular disease and diabetic nephropathy (antihypertensive medication, statins)

■ Screening for diabetic retinopathy for prevention of blindness

■ Interventions to prevent foot ulcers/amputation

■ Interventions in diabetes-related emergencies

The questions and outcomes identified as critical or important were peer reviewed and modified by 4 external experts. The outcomes are presented in the GRADE Tables.

Identification and generation of evidence

The following databases were searched for systematic reviews published up to December 2010:

■ Medline/Pubmed

■ Embase

■ DARE

■ Cochrane Database of Systematic Reviews

Identified systematic reviews were considered suitable if they were up-to-date in 2008 or later, and if they scored 8 or more on the 11-point AMSTAR tool for assessing the quality of systematic reviews (*5*). If more than one acceptable systematic review was identified, the most recent one was used, unless data on one or more outcomes of interest were available only in the earlier review. The outcomes in the scoping questions matched those defined in the systematic reviews, with very few exceptions.

Systematic reviews of acceptable quality but published or updated before 2008 were updated using the same search strategy and study inclusion criteria as the original review and re-running the meta-analysis including the newly identified study/studies, if any (Table 1).

Where no suitable systematic reviews were identified in the literature search, they were commissioned from Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA and Health Management and Policy, and VA Center for Practice Management and Outcomes Research at the University of Michigan, An Arbor, Michigan, USA. Systematic reviews were not commissioned for interventions where no RCTs or observational studies were conducted and for interventions for which the group concluded that currently recognized treatment effects are unlikely to be confused with other effects or biases (e.g. administration of glucose in hypoglycaemia).

The identified and commissioned systematic reviews were used for assessing the quality of the evidence and summarizing the findings in GRADE tables. GRADE tables were not prepared for case series or reports, nor studies of laboratory analytical equivalence.

Existing evidence-based guidelines for diabetes prevention, diagnosis and management were reviewed (NICE (*6*), Canadian Diabetes Association (*7*), American Diabetes Association (*8*), Scottish Intercollegiate Guidelines Network (*9*)), as well as the international guideline developed by the International Diabetes Federation (IDF) for prevention and management of type 2 diabetes (*10*). These guidelines contain a broad range of interventions, and, with the exception of the IDF guideline, appropriate for a high-resource setting. However, some of the interventions are feasible in low-resource settings and were considered for this guideline.

Formulation of recommendations

The recommendations were formulated by the WHO secretariat and discussed at a group meeting. They are based on the GRADE evidence tables which also include assessment of the risk of serious side-effects of treatment. The group gave special consideration to the feasibility of the guideline implementation in low-resource settings. Consensus was a priori defined as agreement of at least 4 group members (majority). Any strong disagreements would have been reported in this document, but consensus was reached on every recommendation and there was no need for voting.

Risks and benefits

The alternative for most of the recommendations in low-resource settings in primary care is usually no intervention. The consequences of untreated type 2 diabetes have been inferred from trials data on patients that did not achieve improvement in established risk factors for complications, and there is no doubt that diabetes substantially increases the risk of premature mortality, limb amputation, blindness and kidney failure (*11*).

There are no data on individual diabetic patient values and preferences in low resource settings, and they could vary between populations. However, the group agreed that early death, heart attacks, strokes, limb amputation, blindness, kidney failure would generally be perceived as important outcomes to be avoided. Overall, although there is some doubt over precision in some interventions, the recommended interventions potentially decrease the risk of these outcomes by 10-40% which was judged to be a treatment effect of relevant size. Furthermore, the interventions have been in widespread use for many years and potential harm of treatment was judged to be acceptable when contrasted with the benefits. More detailed consideration of risks and harms can be found in Annex 2.

Strength of recommendations

For recommendations developed by the GRADE process the strength of the recommendation was based on the quality of evidence, balance between desirable and undesirable effects and cost. The values and preferences are those of the group members as data on the diabetic population in low-resource settings area scarce and likely differ between cultures.

Strong: Moderate or high quality evidence of effectiveness for at least one critical outcome, desirable effects judged to outbalance the undesirable or very low quality evidence on undesirable effects; low cost and feasibility in low-resource settings; can be adopted as policy in most settings.

Weak/conditional: low or very low quality evidence of effectiveness for all critical outcomes, small benefits or harms judged to dominate over benefits, questionable feasibility, lack of follow-up interventions at higher levels of health care.

Peer review

The draft document was sent to 6 peer reviewers (see CD). There was general agreement on the recommendations, but some modifications were suggested. Treatment with sulfonylurea was added at the reviewers' request. The guideline development group accepted

the suggestion of one reviewer to draw attention to medication that has known unfavourable interaction with antiretroviral treatment because the guideline is likely to be used in populations with a high prevalence of HIV infection and antiretroviral treatment. Two reviewers had serious reservation over the feasibility of statin treatment initiated at the primary care level, and this is reflected in the weak strength of the recommendation. Use of insulin was also suggested by some peer reviewers for inclusion, but was not included because of general unavailability of insulin in primary care in low-resource settings. While there was general agreement that insulin should be available in primary care for people already on insulin treatment, the guideline group agree that initiating insulin treatment would be too complex for most primary care settings.

Some reviewers suggested recommending aspirin for primary prevention of cardiovascular disease, but the group agreed that this recommendation is insufficiently supported by evidence and that potential harm was not negligible, so it was not included.

Adaptation and implementation

WHO will provide technical assistance to national guideline expert groups in developing simple management algorithms based on the guideline (see integrated protocols and other tools for Best Buys and WHO Package of Essential Noncommunicable Disease in CD, to facilitate guideline implementation in primary care). Workshops for training primary health care teams and policy makers on the use of the management protocols will be conducted in every low-income country that decides to integrate NCD prevention and management into primary care services. The proposed interventions present a minimum for improving diabetes care at the primary care level and should be applicable in all countries. However, the treatment protocols based on the guideline might nevertheless need to be specific to the local situation, depending on the availability of technology and medication.

Update

The guideline will be updated in 2016, unless made seriously obsolete earlier by breakthrough research.

Format and dissemination

The guidelines will be printed and available in pdf format on the WHO website. It will also be disseminated through ministries of health to all participants of workshops that will be organized for training primary care staff on the use of management protocols based on the guideline.

Impact and quality of the guideline

Initially, the effect of the guidelines will be assessed through process indicators by the ministries of health and technical help from WHO (e.g. number of low-income countries that introduce diabetes management at the primary care level, people with diabetes diagnosed in primary care, number of referrals for fundus examination, availability of essential medication at primary care level).

Countries will also be given technical assistance to monitor disease outcomes and indicators, depending on availability of resources for NCD surveillance (e.g. proportion of diabetic patients with adequate glycaemic control, incidence of acute complications, rates of limb amputations, etc.).

Recommendations and evidence

A. Diagnosing diabetes

Diabetes is diagnosed by laboratory measurement of plasma glucose in a blood sample. Diagnostic cut-off values are presented in Table 1 (*12*). Fasting capillary glucose is likely to be the most feasible measurement in low-resource settings.

The guideline development group agreed that all people 40+ years old should have the following measurements: waist circumference, blood pressure, fasting or random plasma glucose, urine protein, urine ketones in newly diagnosed diabetes, plasma cholesterol if the test is available and testing of foot pulses and sensation if known to have diabetes.

Table 2. Current WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycaemia

Diabetes	
Fasting plasma glucose	≥7.0mmol/l (126mg/dl)
2-h plasma glucose*	**or**
	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l (126mg/dl)
2-h plasma glucose*	**and**
	≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl)
2-h plasma glucose*#	**and (if measured)**
	<7.8mmol/l (140mg/dl)

*   Venous plasma glucose 2-h after ingestion of 75g oral glucose load

If 2-h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

In first-contact health services in low-resource setting laboratory measurement of plasma glucose is not available and patients need to be referred to the next level of care for diagnosis. This is often impractical and costly. The guideline panel considered the use of hand-held devices that measure blood glucose in a capillary blood sample. These devices are currently widely used for self-monitoring of glycaemia in persons with diagnosed diabetes, but are not routinely used for diagnosing diabetes.

Question: Can point-of-care devices be used for diagnosing diabetes in the absence of laboratory facilities?

Recommendation

> 1. Point of care devices can be used in diagnosing diabetes if laboratory services are not available.
>   Quality of evidence: not graded
>   Strength of recommendation: strong

A systematic review evaluating diagnostic accuracy of hand-held devices is the basis for this recommendation (SEE: Systematic review Echouffo Tcheugui JB et al). Two kinds of studies were identified – studies of analytical accuracy and epidemiologic studies of diagnostic performance. Results obtained by hand-held devices showed good agreement with those obtained by laboratory methods on the same sample, but the level of analytical accuracy varied with respect to standards defined by several professional organisations, and there is no single set of assessment criteria.

The epidemiological studies were not suitable to answer the question on the sensitivity and the specificity of measurement by hand-held devices in diagnosing diabetes because none of the studies compared blood glucose values obtained by 2 methods in the same blood sample. Therefore, a GRADE table for the evidence was not produced. The recommendation is based on studies of accuracy of biochemical methods used by currently available point of care devices..

B. Glycaemic control

Lowering of plasma glucose towards normal values relieves symptoms of hyperglycaemia and has a beneficial effect on macrovascular and microvascular complications.

The evidence on improved cardiovascular outcome comes from a meta-analysis of randomized controlled trials designed to estimate the effects of more intensive glucose control compared to less intensive control on the risk of major cardiovascular events in patients with type 2 diabetes (*14*). Various pharmacologic agents were used to lower plasma glucose in these studies.

There is evidence of moderate quality that lowering glycaemia has a modest beneficial effect on cardiovascular disease risk (9% reduction). This is supported by the follow-up of the UKPDS participants 10 years after the study was closed (*15*). No effect on overall mortality was shown.

The evidence for beneficial effect of glucose lowering on microvascular complications come from several RCTs. The Diabetes Control and

Complications Trial (DCCT) has shown that better glycaemic control reduces the risk of microvascular complications in type 1 diabetes (*16*) and subsequent epidemiological follow-up of the trial cohort suggests that the risk of macrovascular complications is reduced as well by intensive glucose control (*17*). In the ADVANCE trial major microvascular outcomes (new or worsening retinopathy or nephropathy) were reduced by 14% in the intensively treated group (*18*).

The VADT trial did not find a reduction of macrovascular and microvascular complications with intensive glucose control, but found a slower progression of albuminuria in the intensively treated group (*19*). The UKPDS found a 25% relative risk reduction in aggregate microvascular endpoints in the intensively treated group (*20*).

The guideline development group consensus was that patients with newly diagnosed diabetes and urine ketones 2+ or with newly diagnosed diabetes in lean persons <30 years should be referred to a higher level of care.

Advice on diet and physical activity

The majority of persons with Type 2 diabetes are overweight or obese, which further increases their risk of macrovascular and microvascular complications through worsening of hyperglycaemia, hyperlipidaemia and hypertension. (*21*)

Questions: Does advice on diet and physical activity improve outcomes in diabetic patients?

Does low glycaemic-index food improve outcomes in diabetic patients?

Recommendations

1. Advise overweight patients to reduce weight by reducing their food intake.
   Quality of evidence: very low
   Strength of recommendation: conditional

2. Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
   Quality of evidence: moderate
   Strength of recommendation: conditional

3. Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g walking).
   Quality of evidence: very low
   Strength of recommendation: conditional

There is strong evidence that type 2 diabetes can be prevented or delayed in persons at high risk by repeated counselling on weight-loss and increasing physical activity. The evidence on what dietary advice is effective once type 2 diabetes is diagnosed is less clear. The evidence on important outcomes is either very low (glycaemic control, intentional weight loss) or not available (risk of chronic complications and quality of life).

The evidence for these recommendations comes from a Cochrane review of randomised trials that compared different dietary advice and approaches (*22*). Very little data could be integrated with a meta-analysis and none of the studies examined long-term outcomes. There is some indication that better glycaemic control, as measured by glycated haemoglobin (HbA1c) could be achieved when dietary advice is combined with advice on exercise. None of the trials included in the Cochrane review had a control group which received no advice at all, which is the current reality in most low-resource settings. Despite the low quality of the evidence, advice on diet and physical activity is recommended as the intervention is deemed feasible, is low-cost, has a low risk of adverse events and not been proven to be ineffective by high quality evidence. The recommendation on favouring foods with a low glycaemic index is based on a systematic review that found a favourable effect of such a diet on glycaemic control (*23*). However, no studies were conducted in low-resource settings and the concept of the glycaemic index might be too complex for this diet to be feasible in areas of low literacy and basic health services.

Diabetes is a progressive illness. Introduction of oral hypoglycaemic agents (OHA) will often be necessary in patients on diet treatment only, and the dosage further increased to improve glycamic control. In studies of where intensive glycaemic control was compared with less intensive control in patients with type 2 diabetes, there was no glycaemic control threshold effect for complications. However, it was shown that patients who achieved HbA1c values of 7% or below had a significantly lower risk of microvascular complications than did less intensively treated patients who achieved a higher mean HbA1c value (7.9-9.4%) (*18*;*19*;*24*). An HbA1c value of approximately 7% is associated with fasting plasma glucose concentration of approximately 6.5mmol/l (*25*).

Metformin

Question: Can metformin be used as first-line oral hypoglycaemic agent in patients with type 2 diabetes?

Recommendation

> **1.** Metformin can be used as a first-line oral hypoglycaemic agent in patients with type 2 diabetes who are not controlled by diet only and who do not have renal insufficiency, liver disease or hypoxia.
> Quality of evidence: very low
> Strength of recommendation: strong

The evidence for this recommendation comes from a Cochrane review of randomised-controlled trials (RCT) (*26*). The daily dose of metformin was 1-3g and titrated clinically. The results for the comparison between metformin and diet or metformin and placebo were presented and analysed separately for the United Kingdom Prospective Diabetes Study (UKPDS) (*27*) because of its considerably longer follow-up and differences in reporting primary outcomes compared to the other included trials that compared metformin to diet or placebo.

Only a small number of studies reported patient-important outcomes such as death, major morbid events (e.g. stroke, myocardial infarction, amputation, blindness, renal failure) and quality of life. The majority of studies reported surrogate outcomes that indicate increased risk for important outcomes (e.g. HbA1c, cholesterol, retinopathy or nephropathy progression) or laboratory outcomes (e.g. C-peptide levels). The data on morbidity and mortality come largely from the UKPDS.

Data on lactic acidosis, a serious side-effect of fenformin use and by analogy feared to be caused by metformin as well come from a Cochrane review of RCTs and observational studies (28). It provides high quality evidence that the risk of this complication is low and not higher than with other hypoglycaemic agents. However, although 97% of the studies included in the systematic review did include patients with at least one of the standard contraindications for metformin (renal insufficiency, cardiovascular diseases, liver diseases, pulmonary disease), the review was not able to quantitatively assess the safety of metformin treatment in the presence of each of these hypoxic co-conditions. More research on the risk of lactic acidosis with metformin use in these particular populations is needed. If in doubt over the presence of contraindications, the patient should be referred to the next level of care. Metformin should be discontinued during acute severe illness such as pneumonia, severe infection, dehydration, myocardial infarction and the patient referred to the next level of care.

Metformin vs diet only

One arm of UKPDS (UKPDS 34) allocated overweight and obese patients to either metformin or diet only (*27*). Patients allocated to metformin had a significantly lower risk of any diabetes-related death and

macrovascular and microvascular outcome (RR 0.74, 95% CI 0.60-0.90). All-cause mortality was also significantly lower in patients in the metformin arm of the trial (RR 0.68, 95% CI 0.49-0.93). The only other RCT that compared metformin to diet only and reported morbidity and mortality found a higher but statistically nonsignifant risk of ischaemic heart disease in patients treated with metformin (RR 3.0, 95% CI 0.13-71.92) (*29*). Three RCTs comparing metformin with diet reported glycated haemoglobin (HbA1c) (*27;29;30*). Metformin-treated patients had a significantly lower mean HbA1c value (Standardised mean difference -1.06, 95% CI -1.89 to -0.22). Data on adverse events was available only for hypoglycaemia which was recorded in two RCTs and the risk was found to be increased.

Metformin vs placebo

Six RCTs recorded adverse events (hypoglycaemia, diarrhoea, gastrointestinal disturbances). Diarrhoea was found to be more frequent with metformin than with placebo, but was not life-threatening. Hypoglycaemia and gastrointestinal does not appear to be more frequent with metformin.

Overall, this recommendation is based on moderate quality evidence that metformin lowers blood glucose, as measured by HbA1c. The evidence on other, potential, beneficial effects of metformin on long-term microvascular and macrovascular complications is of low or very low quality, or not available.

Sulfonylureas

Question: Can sulfonylurea be used as first-line oral hypoglycaemic agent in patients with type 2 diabetes?

Recommendation

> **1.** Give a sulfonylurea to patients who have contraindications to metformin, or in whom metformin does not improve glycaemic control.
> Quality of evidence: very low
> Strength of recommendation: strong

This recommendation is derived from a systematic reviews of RCTs that compared effectiveness and safety of metformin and sulfonylureas (*31*). There were 17 trials that compared glycaemic control and overall metformin and sulfonylureas were shown to perform similarly in lowering HbA1c. The evidence on similar levels of glycaemic control (HbA1c) achieved with metformin and sulfonylureas is of high quality.

There are fewer trials that compared metformin and sulfonylurea and examined important long-term outcomes such as cardiovascular disease and microvascular complications. The systematic review did not pool the results for some of the outcomes because of substantial methodological diversity (e.g. different dosage and definitions of outcomes), or lack of trial data to combine. Five RCTs reported on all-cause mortality and found a small effect that favours metformin (*32-36*), but the evidence is of low quality.

Two RCTs reported on cardiovascular outcomes, but they were not a primary outcome in either (*33;37*). The evidence of low quality does not favour either drug. No RCT evaluated the progression of retinopathy. One RCT examined the effect of metformin and sulfonylurea on the glomerular filtration rate and progression of microabluminuria, but did not compare the two treatment groups directly (*38*).

There is high quality evidence from nine RCTs that the risk of hypoglycaemia is higher with sulfonylureas than with metformin (*32;34;39-45*).

Table 2: Sulfonylureas used in clinical trials included in the systematic review (31)

Sulfonylurea	Daily dosage (mg)	Duration of action
Glibenclamide	2.5-15	Intermediate to long
Glipizide	2.5-20	Short to intermediate
Gliquidone	15-180	Short to intermediate
Gliclazide	40-320	Intermediate
Glimepiride	1-6	Intermediate

First generation sulfonylureas (tolbutamide, chlorpropamide) were not included in the systematic review.

Glibenclamide is a second generation sulfonylurea and the only sulfonylurea on the WHO Essential Medicine List. Thus it is most likely to be available in low-resource settings. As precaution against severe hypoglycaemia, glibenclamide should be started with a small dose of 2.5-5 mg once daily with breakfast, and adjusted according to response to a maximum of 15 mg daily (*46*).

The guideline development group consensus was that patients with fasting plasma glucose >14 mmol/l despite maximal doses of metformin and sulfonylurea should be referred to the next level of care.

C. Reducing the risk of cardiovascular disease and diabetic nephropathy

Nephropathy

Morbidity and mortality from cardiovascular disease (CVD) are two to five times higher in persons with diabetes compared to people without diabetes (*47*), and diabetes confers about a two-fold excess risk for a wide range of vascular diseases, independently from other conventional risk factors (*48*). Treatment recommendations are based on the level of CVD risk as estimated by the WHO CVD risk-assessment tool (*49*).

Diabetic nephropathy occurs in about 25% of people with type 2 diabetes (*50*), and a substantial proportion progresses to end-stage renal disease (*51*).

Statins

Question: Should statins be given to patients with type 2 diabetes for primary prevention of CVD?

Statins (3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors) have been found to reduce CVD risk in persons at high risk. A recent meta-analysis combining the results of 76 randomized trials of statins in primary and secondary prevention of CVD concluded that statins have a beneficial effect on all-cause mortality, revascularisation, risk of myocardial infarction and stroke, and cause relatively mild adverse events (*52*). Much of statins' therapeutic effect is believed to come from its lowering of low-density lipoprotein, but there is some evidence of other, possibly lipid-independent, beneficial effects on blood vessels (*53*).

Recommendation

> **1.** Give a statin to all patients with type 2 diabetes aged ≥ 40 years.
> Quality of evidence: moderate
> Strength of recommendation: conditional

Table 3. Statins used in clinical trials with diabetic patients included in the systematic review (54)

Statin	Daily dosage (mg)
Lovastatin*	20-40
Simvastatin*	40
Pravastatin	10-40
Atorvastatin	10
Glimepiride	1-6

* Contraindicated in HIV positive patients receiving protease inhibitors or ritonavir (*55;56*).

Despite the availability of generic statins, their cost could still make their availability in low-resource settings uncertain, or their introduction into primary health care could reduce the population coverage by more affordable essential medication such as antihypertensives and metformin. Therefore, the recommendation is conditional on availability of resources for statins, after complete coverage by metformin, sulfonylureas and antihypertensives.

The evidence for this recommendation comes from a meta-analysis of randomized controlled trials of statins in the primary prevention of CVD in people without established cardiovascular disease but with CVD risk factors, one of which is diabetes (*54*). The meta-analysis was conducted for major patient-important outcomes such as total mortality, major coronary heart disease events, stroke and serious adverse events such as cancer and did not include studies with surrogate outcomes such as vascular changes. The meta-analysis included large trials that included diabetic patients only (CARDS) (*57*), ASPEN (*58*), HPS (*59*), and data from a large diabetic subgroup of the ASCOT-LLA study, a trial of statins in people with different CVD risk factors such as hypecholesterolaemia, hypertension and high LDL- cholesterol (*60*). There were two trials with diabetic patients only that reported all cause mortality, one reported a statistically insignificant reduction (CARDS), while the other reported a non-significant increase (ASPEN). All the trials included patients aged 40 years and older, predominantly male and of European origin, although some ethnic groups were also included.

Trials which reported the outcome of major coronary events in diabetic patients showed a 17- 36% reduction in the odds in people receiving statins (CARDS, ASCOT-LLA, HPS). Separate synthesis was not presented for people with diabetes, but the meta-regression analysis found no heterogeneity of statin effect in subgroups dichotomised by sex, age and presence of diabetes (*54*). A subsequent meta-analysis

of controlled trials of statins in both primary and secondary prevention of CVD confirmed the findings that statins offer benefits in people at high risk of CVD, including people with diabetes and that the effect of several currently available statins was similar (*61*). The meta-analysis also demonstrated an increased risk of elevated liver enzymes but not an increased risk of important clinical events, except for an increased risk for diabetes (*52*). However, if available, liver function laboratory testing should be performed before introducing statin treatment.

In the GRADE evidence profile pooled data from studies conducted on diabetic patients without cardiovascular disease provide moderate quality evidence that administration of statins to people with diabetes reduces mortality, the risk of coronary events and stroke and is unlikely to substantially affect the short-term risk of cancer and death due to all causes.

Antihypertensive treatment

Blood pressure lowering in diabetic patients reduces the risk of microvascular and macrovascular complications (11;62;63).

Question: What are the target blood pressure targets to improve outcomes in patients with type 2 diabetes?

Recommendations

Target blood pressure values

1. The target value for diastolic blood pressure in diabetic patients is ≤80mmHg.
   Quality of evidence: moderate
   Strength of recommendation: strong

2. The target value for systolic blood pressure in diabetic patients is <130mmHg
   Quality of evidence: low
   Strength of recommendation: weak

The evidence for the recommended target for diastolic blood pressure comes from two randomized controlled trials. The diabetes arm of the Hypertension Optimal treatment (HOT) Trial showed clinically important reductions in cardiovascular mortality and major cardiovascular events in the group with diastolic blood pressure ≤80 mmHg, compared to those with ≤90 mmHg. (*64*). The UKPDS found a reduction in progression of microvascular disease, risk of stroke and risk of any diabetes related end-point in the group assigned to tight blood pressure control which achieved a mean diastolic blood pressure of 82 mmHg. (*65*). The GRADE table shows a meta-analysis of the study

results which provides high quality evidence that tighter diastolic blood pressure control reduces overall mortality, and moderate quality evidence that it reduces the risk of myocardial infarction, stroke and progression of microvascular complications in people with type 2 diabetes.

The recommended target of <130 mmHg for systolic blood pressure is based on evidence from two randomized controlled trials (*66;67*) and one prospective cohort study (*62*). The recommendation is based on moderate quality evidence that systolic blood pressure <130 mmHg offers some protection against stroke. The evidence on the beneficial effect of blood pressure <130mmHg on mortality and myocardial infarction is of low quality. In an epidemiological analysis of the UKPDS trial, lowest risk of death, coronary heard disease and microvascular complications was observed in study participants with a systolic blood pressure <120 mmHg (*62*). In the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) randomized controlled trial the participants in the moderate treatment arm achieved mean systolic blood pressure of 137 mmHg and those in the intensive treatment arm achieved 128 mmHg. The primary outcome was creatinine clearance and no difference between the two treatment arms was seen in this outcome. However, there was statistically significant reduction in risk of retinopathy progression and stroke (*67*). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a randomized trial designed to test the effect of a target systolic blood pressure <120 mmHg on major cardiovascular events. The mean systolic blood pressure was119.3 mmHg in the intensive intervention group and 133.5 mmHg in the standard treatment group. No significant difference between the two intervention groups was found in all-cause death rates, nor in a composite outcome of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. The intensive treatment group had a significantly lower risk of stroke (*66*). Serious events that necessitated hospitalization, are life-threatening or cause permanent disability were recorded. The intensively treated group had a higher incidence of hypotension, bradycardia or arrhythmia and hyperkalaemia, but the absolute risk of these adverse events was low (*68*). In the HOT study systolic blood pressure was consistently underestimated in the measurement and it is therefore difficult to use the data. In the UKPDS, the mean systolic blood pressure in the group with tight blood pressure control was 144 mmHg, and 154 mmHg in the group with less tight control. (*69*)

The guideline development group consensus was that patients with diabetes proteinuria or blood pressure >130/80 mmHg despite treatment with 2 or 3 blood pressure lowering agents should be referred to the next level of care.

Choice of antihypertensive agent

Question: Can low-dose thiazides/inhibitors of angiotensin-converting enzyme (ACE-inhibitors)/beta blockers be used to improve outcomes in patients with type 2 diabetes and hypertension?

Recommendations

1. Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined.
Quality of evidence: very low for thiazides, low for ACE inhibitors
Strength of recommendation: strong

2. Beta blockers are not recommended for initial management of hypertension in diabetic patients, but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.
Quality of evidence: very low
Strength of recommendation: strong

Table 4. Antihypertensive agents used in clinical trials included in systematic reviews (70;71)

Agent	Daily dosage (mg)
Thiazides	
hydrochlorothiazide	12.5-25
chlorthiazide	500-1000
trichlormethiazide	1-4mg
ACE inhibitors	
enalapril	5-40
lisinopril	10-20
ramipril	2.5-20
captopril	50-100
cilazapril	2.5-10
fosinopril	20-40
trandolapril	2-4
perinodopril	2-4
Beta-blockers	
atenolol	50-100
propranolol	2-4

The evidence for these recommendations comes from a Cochrane review of randomized placebo- or untreated group - controlled trials of at least one year duration (*70*), and is supported by the results of a RCT not included in the review (*72*). The Cochrane review did not separately analyse data from diabetic patients, but some of the included trials were on diabetic patients only and diabetes was not an exclusion criterion in any of the RCTS included in the meta-analysis. The recommendations are graded as "strong" because the moderate quality evidence

is supplemented by a trial not included in the review because it was a head-to-head comparison of thiazides and ACE inhibitors and showed no significant difference between these two drug groups in the incidence of coronary heart disease. (*72*) There is moderate quality evidence that beta-blockers compared to placebo did not reduce all-cause mortality nor coronary heart disease, but did reduce the risk of stroke. Thus priority is given to low-dose thiazides and ACE inhibitors. In a Cochrane review of the effect of blood pressure lowering agents on pregression of renal complications, ACE inhibitors have additionally been shown to reduce the progression to microalbuminuria in normoalbuminuric diabetic patients (*71*), but this effect has not been examined for thiazides. Although the risk of adverse events was significantly higher with these antihypertensive agents than with placebo, the adverse events were judged to be relatively mild. The choice of antihypertensive medication in low-resource settings is likely to be influenced by local availability and cost. Priority should be given to thiazides and ACE inhibitors.

D. Prevention of lower limb amputations

Diabetes is the leading cause of non-traumatic lower limb amputations (*73*). The lifetime risk of developing foot ulcers in persons with diabetes is about 15% (*74*). These lesions may become infected and ultimately result in amputation because of gangrene.

Question: Does multifactorial intervention with educating patients on foot care and education of health staff to asses risk of foot ulcers reduce the incidence of foot ulcers in patients with type 2 diabetes?

Recommendations

> **1.** Give patients health education on foot hygiene, nail cutting, treatment of calluses, appropriate footwear.
> Quality of evidence: low
> Strength of recommendation: strong
>
> **2.** Educate health care workers on assessment of feet at risk of ulcers using simple methods (inspection, pin-prick sensation).
> Quality of evidence: low
> Strength of recommendation: strong

A high value is placed on avoiding lower limb gangrene and need for amputation.

The evidence used in formulating these recommendations comes from a systematic review (*75*). The review included individual and cluster-randomized clinical trials of combined interventions that included at least two levels of care (the patient, the health care provider, the

health care system). Due to heterogeneity between studies in study interventions, control interventions and health care settings, no synthesis of outcome data was attempted.

The recommendations are supported by low quality evidence from 5 RCTs, none of them conducted in low-resource settings. The recommended interventions were judged to be feasible and low-cost, and are recommended despite the lack of evidence of their effectiveness, as the evidence of no effect was also of low quality. The guideline group judged that the evidence of no effect was insufficient and that research is recommended to increase the body of evidence, particularly in low-resource settings.

The guideline development group consensus was that patients with severe foot infection and/or foot ulcers should be referred to the next level of care.

E. Prevention of blindness

Diabetic retinopathy is a major cause of vision loss worldwide (*76*).

The disease evolves through recognizable stages in its progression to blindness, is an important public health problem and there are effective and accepted screening tests. Timely laser photocoagulation therapy can prevent progression of vision loss (*77*).

Question: What is the recommended frequency of screening for retinopathy to reduce the incidence of vision loss in type 2 diabetic patients by at least 50%?

Recommendation

> **1.** Persons with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed and every two years thereafter, or as recommended by the ophthalmologist.
> Quality of evidence: low
> Strength of recommendation: conditional

This recommendation is based on data from developed countries which show that a substantial proportion of newly diagnosed diabetic patients already have diabetic retinopathy (*78*). The recommended frequency of screening is based on a systematic review of cohort studies, modelling and cost-effectiveness analyses (see systematic review by Echouffo Tcheugui) that examined the effect of different screening intervals on risk of vision loss and costs. The studies were too heterogeneous for quantitative synthesis, and the recommended screening

interval ranged from one to four years. A one-year screening interval is unlikely to be feasible in low-resource settings.

Authors of studies that compared a 2-year interval with a 1-year interval are largely in agreement that a 2-year interval is acceptable as the risk of missing sight-threatening retinopathy is low. The largest cohort study, conducted in the United Kingdom and following 20,778 diabetic patients for 17 years found an odds ratio of 0.93 (95%CI: 0.82–1.05) when comparing incidence of sight-threatening retinopathy in patients screened every 1 year to the incidence in patients screened every 2 years (*79*). An interval of more than 24 months was associated with an increased risk (OR=1.56, 95% CI: 1.14-1.75) However, all the cohort studies were conducted in developed countries.

Unfortunately, many low-resource settings do not have the laser equipment for photocoagulation of retinal/macular lesions for treating sight-threatening retinopathy, hence the weak/conditional recommendation.

The guideline development group consensus was that diabetic patients with recent deterioration of vision or no retinal exam in 2 years should be referred to the next level of care.

F. Severe hypoglycaemia

Hypoglycaemia (low blood glucose) is a frequent complication in diabetic patients receiving medication to lower blood glucose, particularly sulfonylurea and insulin. The brain requires a continuous supply of glucose and this is dependent on arterial plasma glucose concentrations (*80*). Severe hypoglycaemia is defined as hypoglycaemia where the patient is unable to self-treat (*81*). It can cause loss of consciousness and coma, lead to neuronal death and is potentially life-threatening (*82*). The functional brain failure caused by hypoglycaemia is corrected after blood glucose concentration is raised. This can be accomplished by ingestion of carbohydrates, if that is feasible or parenteral glucose if not feasible.

Question: What is the recommended intervention in severe hypoglycaemia?

Recommendations

1. Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 should be given hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.
Quality of evidence: strong
Strength of recommendation: strong

2. Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 mmol/L administer intravenously 20 to 50ml of 50% glucose (dextrose) over 1 to 3 minutes. If not available, substitute with any hypertonic glucose solution. Food should be provided as soon as the patient can ingest food safely.
Quality of evidence: very low
Strength of recommendation: strong

The evidence for this recommendation is derived from animal studies, clinical observations and case reports (*83*;*84*). Although there are no RCTs or observational studies to support this recommendation, the group concluded that there is vast clinical experience that shows a very strong effect of oral or parenteral glucose administration to justify the strength of the recommendation (*81*). Parenteral therapy is necessary when the patient is unable or unwilling to ingest glucose or sucrose orally. However, evidence on the recommended oral or parenteral dosage and frequency is of very low quality, as the effects of various doses have not been investigated systematically.

G. Hyperglycaemic emergencies

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state are life-threatening conditions with somewhat different features that require treatment in hospital by experienced staff. Even there, the case-fatality rate can be quite high (*85*). Both conditions are characterised by fluid and electrolyte depletion and hyperglycaemia. In a primary care setting it will usually not be possible to diagnose diabetic ketoacidosis, but it should be suspected in patients with extreme hyperglycaemia. Hyperglycaemia slows gastric emptying, therefore oral rehydration might not be effective, even in patients who are notvomiting (*86*).

Question: What is the optimal fluid replacement regimen in persons with extreme hyperglycaemia?

Recommendation

1. If blood glucose ≥18 mmol(l refer to hospital with i.v. drip 0.9% NaCl 1 litre in 2 hours, continue at 1 litre every 4 hours until hospital.
Quality of evidence: very low
Strength of recommendation: strong

A separate GRADE table was not prepared for this recommendation. While it is reasonable to attempt rehydration in hyperglycaemic dehydrated individuals suspected of having diabetic ketoacidosis, the

rate and quantity of fluid in hyperglycaemia have not been extensively investigated. The recommendation is based on early physiological studies and one randomized clinical trial that compared two rates of physiologic saline infusion on a small sample of patients and favours a slower rate of infusion in achieving electrolyte balance and rehydration in patients without extreme volume deficit (*87*).

See CD for:

- Systematic reviews and GRADE tables, Benefits and harms of recommendations
- Members of the guideline development group

Prevention of Cardiovascular Disease

Pocket Aid for Assessment and Management of Cardiovascular Risk

Introduction

Cardiovascular disease (CVD) is a major cause of disability and premature death throughout the world. The underlying pathology is atherosclerosis, which develops over many years and is usually advanced by the time symptoms occur, generally in middle age. Acute coronary events (heart attacks) and cerebrovascular events (strokes) frequently occur suddenly, and are often fatal before medical care can be given. Risk factor modification can reduce clinical events and premature death in people with established cardiovascular disease as well as in those who are at high cardiovascular risk due to one or more risk factors.

This pocket aid provide evidence-based guidance on how to reduce the incidence of first and recurrent clinical events due to coronary heart disease (CHD), cerebrovascular disease (CeVD) and peripheral vascular disease in two categories of people. They include;

1. People with risk factors who have not yet developed clinically manifest cardiovascular disease (primary prevention).[1]

2. People with established CHD, CeVD or peripheral vascular disease (secondary prevention).[2]

The accompanying World Health Organization/International Society of Hypertension (WHO/ISH) risk prediction charts (see CD and table 1) enable the estimation of total cardiovascular risk of people in the first category. Part 1 document provides guidance on which specific preventive actions to initiate, and with what degree of intensity.

People in the second category have high cardiovascular risk and need intensive lifestyle interventions and appropriate drug therapy as elaborated in Part II of this document. Risk stratification using risk charts is not required for making treatment decisions in them.

Target audience

This pocket aid can be used by physicians and non-physician health workers, at all levels of health care including primary care. Hypertension, diabetes or established cardiovascular disease may be used as entry points for implementation.

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1   World Health Organization. *Prevention of Cardiovascular Disease. Guidelines for assessment and management of cardiovascular risk*. Geneva, 2007.

2   World Health Organization. *Prevention of recurrent heart attacks and strokes in low and middle income populations. Evidence-based recommendations for policy makers and health professionals*. Geneva, 2003.

Settings

Primary care and other levels of care including low resource settings

Resource needs

■ *Human resources*: Medical doctor or trained nurse/non-physician health worker

■ *Equipment*: Stethoscope, accurate blood pressure measurement device[3], measuring tape and weighing scale, equipment for testing urine glucose and urine albumin, and assay of blood glucose and blood cholesterol

■ *Drugs*: Thiazide diuretics, beta blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, aspirin, metformin, insulin, statins

■ *Other facilities*: System for maintaining medical records, referral facilities

What are the goals of implementation?

The goals are to prevent CHD and CeVD events by lowering cardio-vascular risk. The recommendations assist people to:

■ quit tobacco use, or reduce the amount smoked, or not start the habit

■ make healthy food choices

■ be physically active

■ reduce body mass index, waist–hip ratio/waist circumference

■ lower blood pressure

■ lower blood cholesterol and low density lipoprotein cholesterol (LDL-cholesterol)

■ control glycaemia

■ take antiplatelet therapy as recommended.

Who needs referral to a specialist facility ?

Referral is required if there are clinical features suggestive of:

■ acute cardiovascular events such as: heart attack, angina, heart failure, arrhythmias, stroke, transient ischemic attack

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3   Parati G, Mendis S, Abegunde D, Asmar R, Mieke S, Murray A, Shengelia B, Steenvoor-den G, Van Montfrans G, O'Brien E; World Health Organization. Recommendations for blood pressure measuring devices for office/clinic use in low resource settings. *Blood Press Monit.* 2005 Feb;10(1):3-10.

- secondary hypertension, malignant hypertension

- diabetes mellitus (newly diagnosed or uncontrolled)

- established cardiovascular disease (newly diagnosed or if not assessed in a specialist facility).

Once the condition of the above categories of people is assessed and stabilized, they can be followed up in a primary care facility based on the guidance provided. They will need periodic reassessments in speciality care.

Assessing and managing cardiovascular risk in people with risk factors who have not yet developed clinically manifest cardiovascular disease (primary prevention)

When can the decision be made to give drugs even before grading the cardiovascular risk?

Some individuals are at high cardiovascular risk because they have established cardiovascular disease or very high levels of individual risk factors. All of them need intensive lifestyle interventions and appropriate drug therapy[4,5]. They include people:

- with established cardiovascular disease

- without established CVD who have a total cholesterol ≥ 8 mmol/l (320 mg/dl) or low-density lipoprotein (LDL) cholesterol ≥ 6 mmol/l (240 mg/dl) or TC/HDL-C (total cholesterol/high density lipoprotein cholesterol) ratio >8

- without established CVD who have persistent raised blood pressure (>160–170/100–105 mmHg)

- with type 1 or 2 diabetes, with overt nephropathy or other significant renal disease

- with renal failure or renal impairment.

Instructions for using WHO/ISH risk prediction charts

The WHO/ISH risk prediction charts indicate 10-year risk of a fatal or non-fatal major cardiovascular event (myocardial infarction or stroke), according to age, sex, blood pressure, smoking status, total blood cholesterol and presence or absence of diabetes mellitus for 14 WHO epidemiological sub-regions.

There are two sets of charts. One set (14 charts) can be used in settings where blood cholesterol can be measured. The other set (14 charts) is for settings in which blood cholesterol cannot be measured.

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4 World Health Organization. *Prevention of recurrent heart attacks and strokes in low and middle income populations. Evidence-based recommendations for policy makers and health professionals.* Geneva, 2003.

5 World Health Organization. *Avoiding heart attacks and strokes. Don't be a victim protect yourself.* Geneva 2005.

These are less accurate. Both sets are available in colour and shades of black on a compact disc.

Each chart can only be used in countries of the specific WHO epidemiological sub-region as shown in table 1.

The charts provide approximate estimates of CVD risk in people who do not have established coronary heart disease, stroke or other atherosclerotic disease. They are useful as tools to help identify those at high cardiovascular risk, and to motivate patients, particularly to change behaviour and, when appropriate, to take antihypertensive, lipid-lowering drugs and aspirin.

How do you use the charts to assess cardiovascular risk?

(see figure 1)

- First make sure that you select the appropriate charts using information in table 1.

- If blood cholesterol cannot be measured due to resource limitations, the mean cholesterol value for the population can be used.

- Before applying the chart to estimate the 10 year cardiovascular risk of an individual, the following information is necessary:

  - Presence or absence of diabetes[6]

  - Gender

  - Smoker or non-smoker[7]

  - Age

  - Systolic blood pressure (SBP)[8]

  - Total blood cholesterol[9] (if in mg/dl divide by 38 to convert to mmol/l).

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6 A person who has diabetes is defined as someone taking insulin or oral hypoglycaemic drugs, or with a fasting plasma glucose concentration above 7.0 mmol/l (126 mg/dl) or a postprandial (approximately 2 hours after a main meal) plasma glucose concentration above 11.0 mmol/l (200 mg/l)on two separate occasions). For very low resource settings urine sugar test may be used to screen for diabetes if blood glucose assay is not feasible. If urine sugar test is positive a confirmatory blood glucose test need to be arranged to diagnose diabetes mellitus.

7 All current smokers and those who quit smoking less than 1 year before the assessment are considered smokers for assessing cardiovascular risk.

8 Systolic blood pressure, taken as the mean of two readings on each of two occasions, is sufficient for assessing risk but not for establishing a pretreatment baseline.

9 The mean of two non-fasting measurements of serum cholesterol by dry chemistry, or one non-fasting laboratory measurement, is sufficient for assessing risk.

Once the above information is available proceed to estimate the 10-year cardiovascular risk as follows:

Step 1 Select the appropriate chart depending on the presence or absence of diabetes

Step 2 Select male or female tables

Step 3 Select smoker or non smoker boxes

Step 4 Select age group box (if age is 50-59 years select 50, if 60-69 years select 60 etc)

Step 5 Within this box find the nearest cell where the individuals systolic blood pressure (mm Hg) and total blood cholesterol level (mmol/l) cross. The colour of this cell determines the 10 year cardiovascular risk.

Practice points

Please note that CVD risk may be higher than indicated by the charts in the presence of the following:

- already on antihypertensive therapy
- premature menopause
- approaching the next age category or systolic blood pressure category
- obesity (including central obesity)
- sedentary lifestyle
- family history of premature CHD or stroke in first degree relative (male < 55 years, female < 65 years)
- raised triglyceride level (>2.0 mmol/l or 180 mg/dl)
- low HDL cholesterol level (< 1 mmol/l or 40mg/dl in males, < 1.3 mmol/l or 50 mg/dl in females)
- raised levels of C-reactive protein, fibrinogen, homocysteine, apolipoprotein B or Lp(a), or fasting glycaemia, or impaired glucose tolerance
- microalbuminuria (increases the 5-year risk of diabetics by about 5%)
- raised pulse rate
- socioeconomic deprivation.

Table 1. List of WHO/ISH risk prediction charts by epidemiological sub-regions[10] and WHO Member States

WHO/ISH risk prediction charts by epidemiological sub regions		WHO Member States
Africa	AFR D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome And Principe, Senegal, Seychelles, Sierra Leone, Togo
	AFR E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of The Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
The Americas	AMR A	Canada*, Cuba, United States of America*,
	AMR B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts And Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
	AMR D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
Eastern Mediterranean	EMR B	Bahrain, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
	EMR D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
Europe*	EUR A	Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
	EUR B	Albania, Armenia, Azerbaijan, Bosnia And Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan
	EUR C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
South-East Asia	SEAR B	Indonesia, Sri Lanka, Thailand
	SEAR D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
Western Pacific	WPR A	Australia*, Brunei Darussalam, Japan, New Zealand*, Singapore
	WPR B	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

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10 Mortality strata: A: very low child mortality and very low adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality; E: high child mortality and very high adult mortality.

Figure 1. An example of a WHO/ISH risk prediction chart. 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes mellitus.
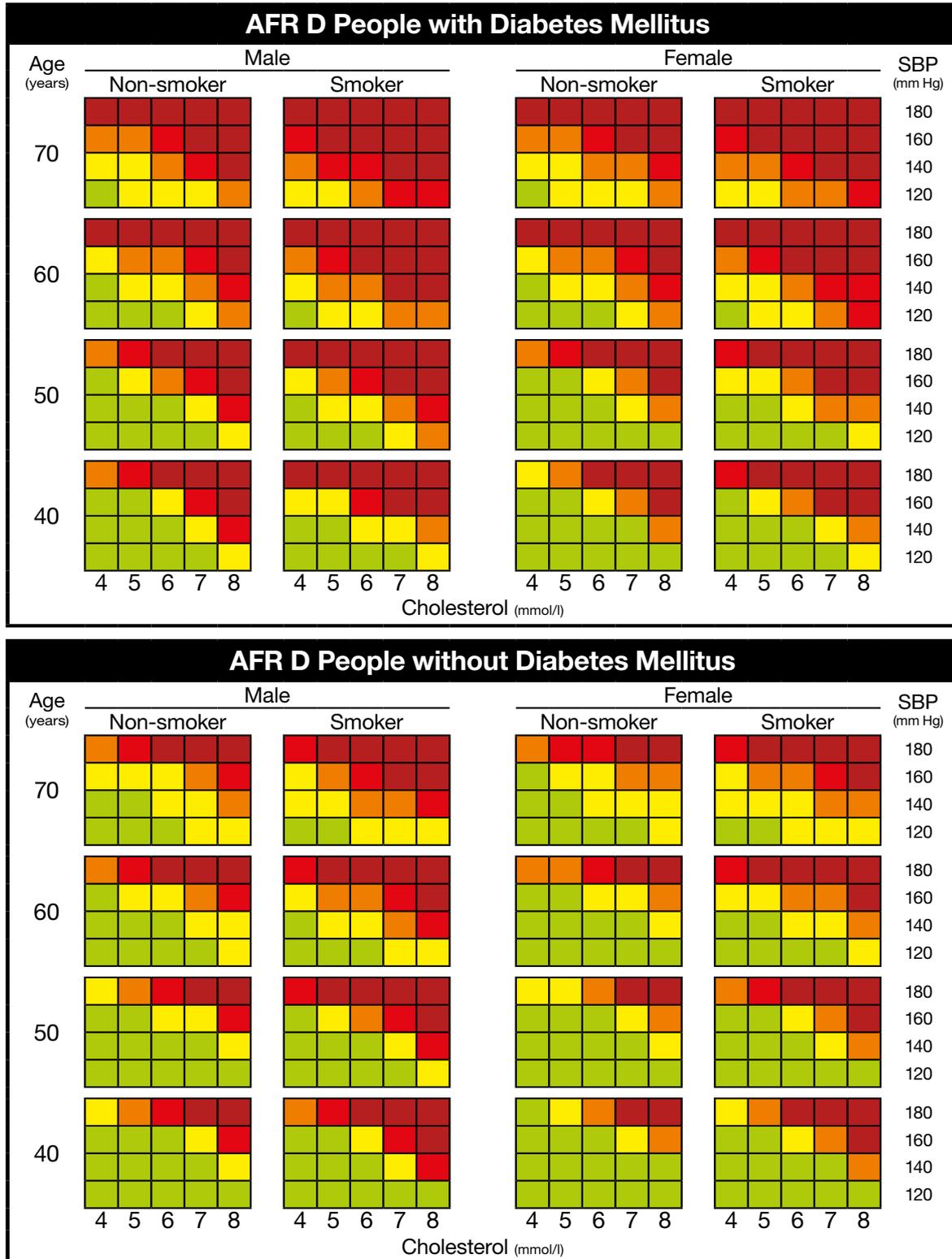
Management of people with established CHD, CeVD or peripheral vascular disease (secondary prevention)

People with established cardiovascular disease (angina pectoris, coronary heart disease, myocardial infarction, transient ischaemic attacks, cerebrovascular disease (CeVD) or peripheral vascular disease (PVD) or after coronary revascularization or carotid endarterectomy) are at very high risk of developing recurrent cardiovascular events. Risk charts are not necessary to make treatment decisions in them.

The goal of management is to prevent recurrent cardiovascular events by reducing their cardiovascular risk.

See CD for:

■ *Prevention of cardiovascular disease, Guidelines for assessment and management of cardiovascular risk*, World Health Organization, 2007

■ *Prevention of recurrent heart attacks and strokes in low and middle income populations*, World Health Organization, 2003

III. Self-care of cardiovascular disease, diabetes and chronic respiratory disease

Abbreviations

AMSTAR	A measurement tool to assess the methodological quality of systematic reviews
BMI	Body mass index
BP	Blood pressure
CCTs	Controlled clinical trials
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ED	Emergency Department
EQ5D	EQ5D measure of quality of life
ER	Emergency room
FEV1	Forced expiratory volume
FVC	Forced vital capacity
GDG	Guideline Development Group
GP	General Practitioner
GRADE	Grading quality of evidence and strength of recommendations
HbA1c	Glycosylated haemoglobin
HCP	Health care professional
HRQoL	Health-related quality of life
IHCAs	Interactive health communication applications
IHD	Ischaemic heart disease
INR	International normalised ratio
IPD	Individual patient data
LMIC	Low to middle income countries
MD	Mean difference
METS	Metabolic Equivalent of Tasks

MI	Myocardial infarction
mmHg	Millimetres of mercury
NCDs	Non-communicable diseases
NGOs	Non governmental organisations
NIHR	National Institute for Health Research
NNT	Number needed to treat
NS	Non significant
O2	Oxygen
OR	Odds ratio
PMD	Pooled mean difference
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SBP	Systolic blood pressure
SE	Standard error
SMBG	Self-monitoring of blood glucose
SMD	Standardised mean difference
SMS	Short messaging service
US	United States
WHO	World Health Organisation
WMD	Weighted mean difference

Executive Summary

"Self-care is the ability of individuals, families and communities to promote health, prevent disease, and maintain health and to cope with illness and disability with or without the support of a health-care provider"

Current epidemiological evidence indicates four non-communicable diseases (NCDs) make the largest contribution to mortality in the majority of low and middle income countries (LMIC), namely: cardio-vascular disease, diabetes, cancer and chronic respiratory disease.

Self-care strategies include both self-care and self-management by the individual. Inherent in the concept is the recognition that whatever factors and processes may determine behaviour, and whether or not self-care is effective and interfaces appropriately with professional care, it is the individual person that acts (or does not act) to preserve health or respond to symptoms.

Self-care involves the entire body of health decisions that individuals make for themselves and their families to maintain physical and mental well-being. Self-care includes a variety of strategies such as staying fit and healthy, both physically and mentally, avoiding hazards such as smoking and improved management of long-term health conditions. To achieve these strategies, self-care also includes elements of self-monitoring, self-management and self-medication. In addition, self-care practices in many different societies represent a wide spectrum of options such as using body massage, religious and cultural rituals, and various ceremonies. Thus self-care also includes managing or minimising the way a chronic condition limits an individual's life.

There is growing recognition that all countries face problems with an ageing population and an increase in NCDs accounting for substantial morbidity and increased medical costs. Whilst self-care should not be used to replace the basic components of essential health care, it may offer an approach for countries to optimize management of NCDs and aid well-being. Although self-care interventions have been integrated into various disease management programs, the evidence on the effectiveness of various interventions and the mode of their implementation have not been synthesized. This guideline provides evidence based recommendations in relation to major noncommunicable diseases as highlighted in the NCD Global Action Plan endorsed by the World Health Assembly in 2008..Determining which self-care strategies are underpinned by evidence of effectiveness and gaining an understanding of the barriers to implementation will aid effective delivery of health care for NCDs.

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Guidance on self-care interventions aimed at four shared risk factors – tobacco use, physical inactivity, unhealthy diets and the harmful use of alcohol are addressed in the 2008-2013 action plan for the global strategy for the prevention and control of non-communicable diseases.

To capture the various components of self-care interventions and various modes of their delivery, the Guideline Development Group (GDG) identified nine questions for the development of the self-care in NCDs recommendations. A search strategy was used to initially retrieve evidence of effectiveness from systematic reviews relevant to self-care and NCDs, and each eligible review was rated using the AMSTAR tool.. For all systematic reviews that were included, we searched for clinical trials that were specifically undertaken in LMIC.

We used the GRADE approach for assessing the quality of evidence and deciding the strength of the recommendations. The quality of the evidence presented in the reviews for critical and important outcomes was graded as: high, moderate, low or very low. The strength of a recommendation (strong, weak) takes into account the overall quality of the evidence and the uncertainly about the target population's values and preferences. It reflects the degree of confidence that the benefits outweigh the harms and and the degree to which the intervention has been tested and/or is relevant to LMIC settings in terms of feasibility and resource implications.

Many of the self-care interventions in NCDs identified in the 9 questions are enthusiastically advocated, applied and supported by policy makers, health workers, the educational system and nongovernmental organizations. Many have wide appeal to the general public and patients themselves, and will continue to be applied or demanded. However, very few of those interventions are based on high or moderate quality evidence of their effectiveness, thus strong recommendations in their favour was judged to be inappropriate. On the other hand, there is similar lack of high or moderate quality evidence of no effectiveness, accompanied by considerable uncertainty over harms outweighing benefits. Thus strong recommendations against their use were also felt to be inappropriate, given their popularity and intuitive appeal. This guideline could help re-prioritize on-going self-care interventions, favouring those with a stronger evidence base. It will hopefully spur research activities to provide more evidence on key questions.

Currently there remains the need to identify pragmatic, low cost, feasible interventions underpinned by high quality evidence, particularly in LMIC settings. There is also a requirement to identify the most cost effective and effective individual components and combinations of interventions for self-care in these settings. The guideline gives some recommendations on future research.

Questions

1. In patients with non-communicable diseases do self-care strategies targeted at the community and/or support networks rather than the individual improve outcomes?

Definition: Self-care strategies for NCDs targeted at the community are designed to be delivered beyond health care institutions either by the health care system or by the local community through its members, trained or untrained, paid or unpaid. Self-care interventions delivered through community action can be complementary to conventional health care or stand-alone programmes.

2. In patients with non-communicable diseases do lay led self-management patient programmes improve outcomes?

Definition: Lay led self-management education programmes are highly structured programmes for people with NCDs which are primarily educational, and address self-care of the disease with the majority of course content delivered by lay individuals.

3. In patients with non-communicable diseases do online resources for self-care improve outcomes?

Definition: Online resources for self-care include: health information, interactive health communication applications (web based information packages that can combine health information with at least one component of support, decision support or behaviour change support).

4. In patients with non-communicable diseases do self-monitoring devices improve outcomes?

Definition: On-going management of NCDs often involves monitoring of a biochemical or physical measure (e.g. blood pressure, blood glucose, peak flow). Whilst these measures can be undertaken in the clinic setting they may be self-monitored in the home setting by the patient or within the community and the results communicated to a health professional for on-going management.

5. In patients with non-communicable diseases do mobile telephone and/or telemonitoring interventions targeted at self-care improve outcomes?

Definition: Telemonitoring involves remotely monitoring patients who are not in the same location as the health care provider. Monitoring devices will transmit information on symptoms and/or vital signs via the telephone to a remote monitoring service provider and/or to their health care provider. Telemedicine is a broader concept that includes patient consultations using telecommunications.

6. In patients with non-communicable diseases do self-treatment interventions improve outcomes?

Definition: Self-treatment intervention includes self-monitoring and adjustment of dosage of medicines by the individual based on a pre-specified action plan agreed jointly by a health care practitioner / worker and the patient. A situation can occur in NCD management in which the patient could or will alter the doses and/or frequency of the treatment depending upon the change in the nature, severity of symptoms and/or biochemical markers of a disease under the guidance of a professional health care provider (e.g. physician) with treatment recommendation.

7. In patients with non-communicable diseases do self-care education/information programmes improve outcomes?

Definition: Education is the process of receiving or giving systematic instruction about a specific aspect of disease whilst information is the knowledge communicated about a particular aspect of a disease.

8. In patients with non-communicable diseases do self-care rehabilitation programmes improve outcomes?

Definition: Rehabilitation therapy aims to improve function that has been lost or diminished by disease. Rehabilitation programmes may incorporate exercise and/or information after an event such as a myocardial infarction.

9. In patients with non-communicable diseases do interventions targeted at adherence improve outcomes?

Definition: Patient adherence has been defined as the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider.

No.	Recommendation	Strength of recommendation	Quality of evidence
	1. In patients with non-communicable diseases do self-care strategies targeted at the community and/or support networks rather than the individual improve outcomes?		
1.1	Community interventions can complement primary health care. Structured training for community workers should be undertaken to aid the detection and on-going management for NCDs.	Weak	Very low
R1	Research is needed to identify pragmatic community based interventions for self-care of NCDs in LMIC. Community programmes should be evaluated for their coverage, generalisability, impact and cost effectiveness.		
	2. In patients with non-communicable diseases do lay led self-management patient programmes improve outcomes?		
2.1	The use of highly structured lay led self-management patient programmes for self-care in NCDs is not recommended at the present time for LMIC.	Weak	Very low
R2	Research is needed to evaluate lay led self-management programmes in LMIC, ideally with identification of the active components of such programmes and their feasibility in low resource settings.		
	3. In patients with non-communicable diseases do online resources for self-care improve outcomes?		
3.1	Health care organisations should provide access to user-friendly, valid and reliable online information targeted at NCDs and their management. Online resources could provide some benefit.	Weak	Very low
R3	Research is needed to evaluate interactive health care web resources, particularly in LMIC settings.		
	4. In patients with non-communicable diseases do self-monitoring devices improve outcomes?		
4.1	Self-measurement to monitor blood pressure is recommended for the management of hypertension in appropriate patients where the affordability of the technology has been established.	Strong	Low
4.2	Self-monitoring of blood coagulation is recommended for appropriate patients treated with oral anticoagulation agents, where the affordability of the technology has been established.	Weak	Moderate
4.3	The use of self-monitoring of blood glucose in the management of patients with type 2 diabetes not on insulin is not recommended at the present time because there is insufficient evidence to support such a recommendation.	Weak	Moderate
4.4	People with type 1 and type 2 diabetes on insulin should be offered self-monitoring of blood glucose based on individual clinical need.	Weak	Low
R4	Research is needed to evaluate the impact of self-monitoring, including assessment of the cost-effectiveness in LMIC.		
	5. In patients with non-communicable diseases do mobile telephone and/or telemonitoring interventions targeted at self-care improve outcomes?		
5.1	The use of telemonitoring for self-care in NCDs is not recommended at the present time, because there is insufficient evidence to support such a recommendation.	Weak	Low

No.	Recommendation	Strength of recommendation	Quality of evidence
5.2	The use telehealth for self-care in NCDs is not recommended at the present time, because there is insufficient evidence to support such a recommendation.	Weak	Low
R5	Research is needed to evaluate telemonitoring and telehealth in LMIC, ideally with identification of the active components of such programmes and their feasibility in low resource settings.		
	6. In patients with non-communicable diseases do self-treatment interventions improve outcomes?		
6.1	Self-monitoring of blood coagulation and self-adjustment of dosage in patients receiving oral anticoagulation agents is recommended if affordable and according to an agreed action plan with a health professional.	Weak	Moderate
6.2	Self-monitoring in asthma and COPD and self-adjustment of dosage is recommended according to an agreed action plan with a health professional.	Weak	Very low
6.3	Self-adjustment of diuretics based on body weight monitoring in heart failure is not recommended at the present time.	Weak	Very low
6.4	Self-monitoring and self-adjustment of insulin dosage is recommended in type 1 diabetes according to an agreed action plan with a health professional.	Weak	Very low
R6	Research is needed to establish a consistent evidence base upon which valid recommendations can be made for self-monitoring and self-adjustment of treatments, particularly in LMIC. The research should evaluate risks and benefits, outcomes, cost and quality of life and also acceptability and potential barriers.		
	7. In patients with non-communicable diseases do self-care education/information programmes improve outcomes?		
7.1	Group education programmes, rather than individual education may offer a cost effective strategy to deliver education in LMIC.	Weak	Very low
	8. In patients with non-communicable diseases do self-care rehabilitation programmes improve outcomes?		
8.1	Appropriate patients could benefit from being educated on the benefits of cardiac rehabilitation, and can be encouraged to undertake rehabilitation exercise in the home setting.	Weak	Very low
8.2	Appropriate patients could benefit from being educated on the benefits of COPD rehabilitation , and encouraged to undertake rehabilitation exercise.	Weak	Very low
R7	Research is needed to evaluate the effectiveness of rehabilitation programmes in the home or community across NCDs, particularly in LMIC.		
	9. In patients with non-communicable diseases do interventions targeted at adherence improve outcomes?		
9.A	Strategies to improve adherence should form part of self-care for NCDs. Promotion of self-care in NCDs should take into account patients' beliefs and concerns about medicines, and their effects on adherence.	Strong	Very low
9.1	No single strategy to improve overall adherence is recommended over another.	Weak	Very low
R8	Research is needed on interventions to improve adherence, particularly in LMIC.		

Introduction

Current epidemiological evidence indicates four non-communicable diseases (NCDs) make the largest contribution to mortality in the majority of low and middle income countries (LMIC), namely: cardio-vascular disease, diabetes, cancer and chronic respiratory disease.[1]

There is growing recognition that all countries face the problem of an ageing population and an increase in NCDs accounting for substantial morbidity and increased medical costs.[2] Although self-care should not be used to replace the basic components of essential health care it may offer an approach for countries to optimize management of NCDs and aid well-being. Self-care implementation strategies should reflect the complexity and co-existence of NCDs, aim to avoid vertical programmes and focus on an integrated health care strategy. Self-care should reflect the diversity of health care systems, their context and be sensitive to the resources available. Although self-care interventions have been integrated into various disease management programs,the evidence on the effectiveness of various interventions and the mode of their implementation have not been synthesized. The NCD Global Action Plan endorsed by the World Health Assembly in 20081 highlighted the need for a guideline on self-care that provides evidence based recommendations in relation to major noncommunicable diseases.

Determining which self-care strategies are underpinned by evidence of effectiveness and gaining an understanding of the barriers to implementation will aid effective delivery of health care for NCDs.

"Self-care is the ability of individuals, families and communities to promote health, prevent disease, and maintain health and to cope with illness and disability with or without the support of a health-care provider."[3]

Self-care strategies therefore include both self-care and self-management by the individual. Inherent in the concept is the recognition that whatever factors and processes may determine behavior, and whether or not self-care is effective and interfaces appropriately with

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1   World Health Organization. 2008-2013 *Action plan for the global strategy for the prevention and control of noncommunicable diseases.* http://www.who.int/nmh/publications/9789241597418/en/

2   World Health Organization, *Global status report on noncommunicable diseases,*" World Health Organization, Geneva, Switzerland, 2010.

3   World Health Organisation. 2009. "Self-care in the Context of Primary Health Care". *Report of the Regional Consultation*, Bangkok, Thailand.

professional care, it is the individual person that acts (or does not act) to preserve health or respond to symptoms.[4]

Self-care involves all health decisions that individuals make for themselves and their families to maintain physical and mental well-being. Self-care strategies include a variety of strategies such as staying fit and healthy, both physically and mentally, avoiding hazards such as smoking and improved management of long-term health conditions. To achieve these strategies, self-care also includes elements of self-monitoring, self-management and self-medication.

Self-care practices in many different societies may represent a wide spectrum of options such as using body massage, religious and cultural rituals. Thus self-care also includes managing or minimising the way a chronic condition limits an individual's life in their own social-cultural context.

A broader framework for self–care emphasizes the behavioural and cognitive dimensions. This would then encompass an individual's behaviour towards symptom recognition and evaluation, and decisions to treat by a selection of self-determined actions or to seek appropriate advice regarding subsequent management decisions.

The target audience for this guideline are health care policy makers and health workers, but it will also be useful to researchers and relevant non-governmental organizations.

The update of the guideline is planned in 5-7 years. Given the number of different interventions and critical/important outcomes, it is unlikely that the evidence base of high or moderate quality will increase earlier,

The guideline was funded by WHO funds. No funds from commercial sources were used.

Within WHO activities on improving the management of chronic NCDs at the primary care, regional and country level will be conducted. Workshops will be held to adapt the guideline to local priorities and assist its implementation.

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4   Dean K, Kickbusch I (1995). "Health related behaviour in health promotion: utilizing the concept of self care". *Health Promotion International*, 10(1), 35-40.

Methods

Databases searched (only English language)

CDSR - Cochrane Database of Systematic Reviews (Cochrane reviews) (up to March 2013)

DARE - Database of Abstracts of Reviews of Effects (other reviews) (up to march 2013)

CENTRAL - Cochrane Central Register of Controlled Trials (clinical trials) (up to March 2013)

MEDLINE - Medical Literature Analysis and Retrieval System Online (from 2001 to March 2013)

EMBASE - Biomedical and pharmacological database (from 2001 to March 2013)

The evidence

The five levels of the review process are summarised in Figure 1.

Titles and abstracts of retrieved citations were screened by one reviewer against the inclusion criteria. Any disagreements were resolved by discussion with the Guideline Systematic Review Group Oxford. Full versions of all included studies were obtained.

Full-text articles were retrieved and excluded for one or more of the following reasons: not relevant for self-care, not a review of NCDs, not a systematic review, no clinical outcomes. Each article was screened by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion with the Guideline Systematic Review Group.

Each eligible review was scored by the AMSTAR tool[5]. Systematic reviews were included if the response was "yes" to two essential AMSTAR quality criteria: Question 3: "Was a comprehensive literature search performed?" and Question 7: "Was the scientific quality of the included studies assessed and documented?".

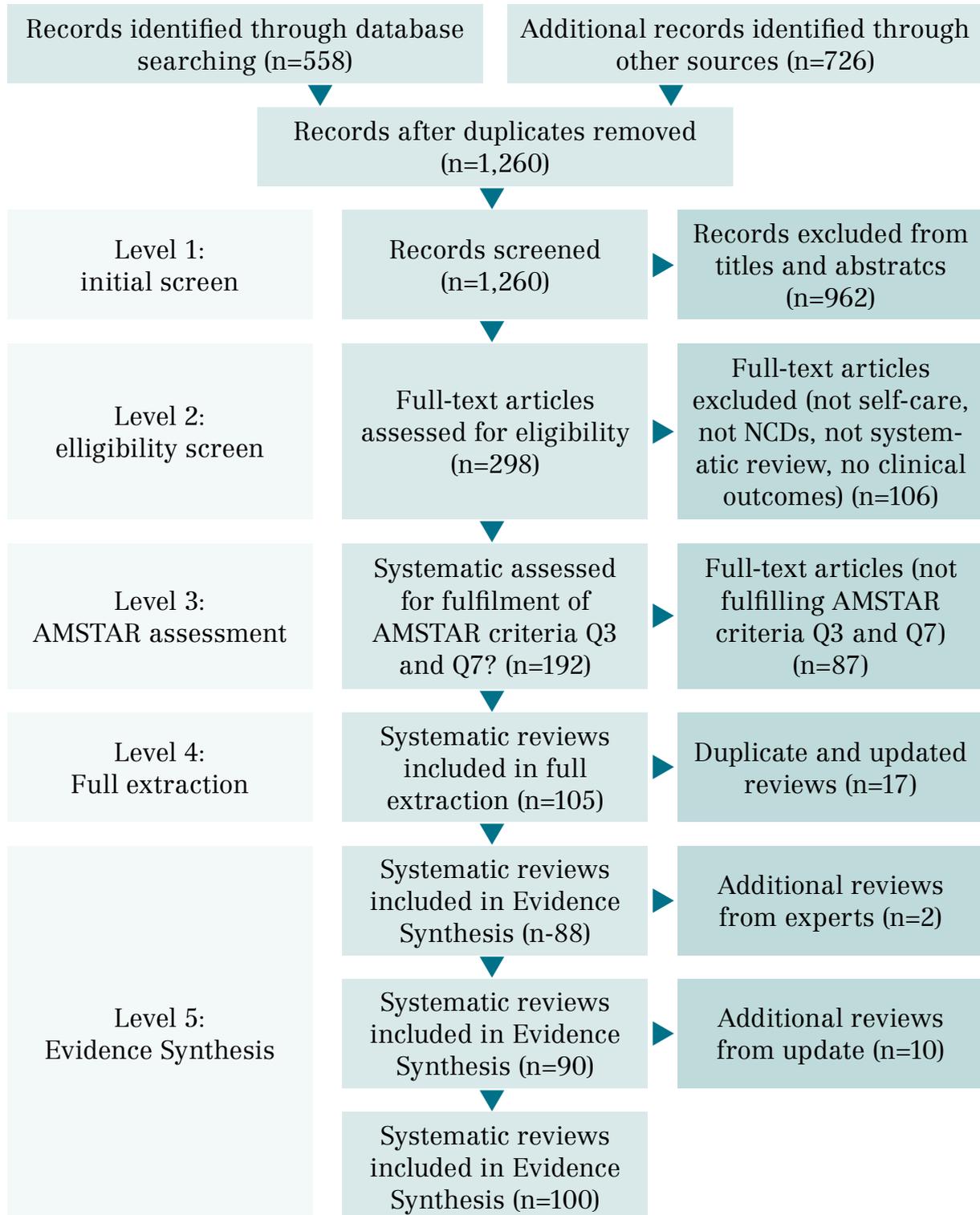Each article was scored by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion with the Guideline Systematic Review Group.".

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5   Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol. 2007 Feb 15;7:10.*

Any disagreements between two reviewers were resolved by discussion with the Guideline Systematic Review Group.

Figure 1. Flow chart WHO self-care guideline*

	Records identified through database searching (n=558)	Additional records identified through other sources (n=726)
	Records after duplicates removed (n=1,260)	
Level 1: initial screen	Records screened (n=1,260)	Records excluded from titles and abstratcs (n=962)
Level 2: elligibility screen	Full-text articles assessed for eligibility (n=298)	Full-text articles excluded (not self-care, not NCDs, not systematic review, no clinical outcomes) (n=106)
Level 3: AMSTAR assessment	Systematic assessed for fulfilment of AMSTAR criteria Q3 and Q7? (n=192)	Full-text articles (not fulfilling AMSTAR criteria Q3 and Q7) (n=87)
Level 4: Full extraction	Systematic reviews included in full extraction (n=105)	Duplicate and updated reviews (n=17)
Level 5: Evidence Synthesis	Systematic reviews included in Evidence Synthesis (n-88)	Additional reviews from experts (n=2)
	Systematic reviews included in Evidence Synthesis (n=90)	Additional reviews from update (n=10)
	Systematic reviews included in Evidence Synthesis (n=100)	

*   References of retrieved systematic reviews that referred to them. References to systematic reviews in publications and guidelines related to self-care.

All reviews relevant to each of the nine questions were summarised for each of the four disease categories.

We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess quality of evidence in the most relevant and/or recent reviews.[6] Several systematic reviews used the standardized mean difference(SMD), as the summary statistic for absolute effect in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways. The standardized mean difference expresses the size of the intervention effect in each study relative to the variability observed in that study:

$$\text{SMD} = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome amon participants}}$$

Thus studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements.[7]

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6 Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knotterus A. GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. 2011;64:380-2.

7 http://handbook.cochrane.org/part_2_general_methods_for_cochrane_reviews.htm

Outcomes

In the full summary GRADE tables (Appendix 4), we presented the effects of interventions on one or more of the following outcomes:

Primary outcomes

- Mortality
- Clinical complications and/or disease progression
- Surrogate outcomes that correlate with clinical complications and/or disease progression (e.g. blood pressure)
- Adherence to treatment

Secondary outcomes

In addition we presented information for the following secondary outcomes:

- Health Related Quality of Life
- Psychosocial outcomes
- Hospitalisation and/or health care utilization
- Cost effectiveness, cost impact, cost savings
- Harms of self-care interventions
- Self-efficacy, knowledge and patient empowerment

See Appendix 1 for GRADE ranking of importance of outcomes.

Formulation of recommendations

The Guideline Development Group (Appendix 3) met twice: once to develop the questions for which recommendations were required and once to review the evidence synthesised and formulate the recommendations.

The recommendations were drafted by the co-chairs of the GDG and the WHO Secretariat. They were then presented and discussed at a meeting of the GDG. They are based on the GRADE evidence tables and the evidence-to-recommendation framework presented for each recommendation in Annex 5. The group gave special consideration to the feasibility of the guideline implementation in low resource settings. Consensus was a priori defined as agreement of the simple majority, without strong objections from the minority. Consensus was reached on every recommendation and there was no need for voting.

Each recommendation was graded as strong when there was confidence that the benefits clearly outweigh the harms (for recommendations to use the intervention), or that harms clearly outweigh the benefits (for recommendations against the intervention). A weak recommendation for an intervention was given when the benefits probably outweigh the harms, but there was considerable uncertainty about the trade-offs, typically due to lack of data. A weak recommendation against an intervention was given when there was considerable uncertainty about the magnitude of benefits and harms.

Peer review

The draft guideline was reviewed by 5 external experts (Appendix 3). The reviewers had a few requests for clarification, but no objections to the recommendations. One reviewer expressed concern that the local decisions on the implementation of the guidelines would not be easy, given that most recommendations were weak for or weak against the intervention. This reviewer questioned the use of GRADE given the general paucity of good quality research, and proposed an alternative method for arriving at the recommendations, but this was not accepted by the GDG.

Declarations of Interest

All the members of the Guideline Development Group, the Systematic Review Group, Observers and Guideline reviewers completed the standard WHO Declaration of Interest Form.

Interest was declared on the WHO forms by the following persons and disclosed orally at the meetings:

Dr William Summerskill is employed by Elsevier, a publisher of several medical journals, as an editor of The Lancet. The GDG approved his participation in the Systematic Review Group.

Dr Richard Chapman had been emplyed by IMS (Intercontinental Medical Statistics) Health. He conducted health economics and outcomes research. His employment ceased 3 months before his engagement in the GDG. The WHO secretariat decided that this did not constitute conflict of interest and that Dr Chapman can participate at all stages of guideline development.

No other participant declared conflict or potential conflict of interest.

All members of the Guideline Development Group participated fully in the discussions and formulation of the recommendations.

Results

We identified 1,260 potential systematic reviews from the searches.

After initial screening we retrieved 298 full-text articles to be assessed for eligibility. Studies were excluded at this stage if they fulfilled one or more of the following conditions: not self-care, not NCDs, not a systematic review or had no clinical outcomes (n=106).

The remaining 192 articles were assessed for quality. Full data extractions were performed for the 88 studies (excluding updated/duplicate studies) fulfilling questions 3 and 7 of the AMSTAR checklist. Two further reviews were identified by experts and an additional ten reviews were identified when the search was updated in March 2013 giving a total of 100 reviews.[1-100] GRADE tables were provided for studies that were the most recent and relevant.

We also identified 87 lower quality reviews.[101-187]

The results are presented below for each of the nine questions.

Question 1: In patients with non-communicable diseases do self-care strategies targeted at the community and/or support networks rather than the individual improve outcomes?

Definition: Self-care strategies for NCDs targeted at the community are designed to be delivered beyond health care institutions either by the health care system or by the local community through its members, trained or untrained, paid or unpaid. Self-care interventions delivered through community action can be complementary to conventional health care or stand-alone programmes.

Summary of evidence

We identified seven systematic reviews of trials of interventions focused on support groups or family members. [17 24 45 53 59 76 92]

One systematic review examined the role of peer support, including one-to-one sessions, self-help or support groups, online computer mediated groups, or peer support within an educational environment for individuals with heart disease, compared with usual care. The six included trials were heterogeneous in intervention and outcomes measured. The trials demonstrated some positive effects of peer support for individuals with heart disease, including higher levels of self-efficacy, improved activity, reduced pain, and fewer emergency room visits. However, the trials had methodological problems: allocation concealment was only clear in one study and high attrition occurred in three.[76]

In a systematic review of various types of social support amongst patients with diabetes, the interventions in the four trials were highly varied and meta-analysis was not possible. One trial showed limited evidence of reduction in HbA1c with patient group consultations to the physician. There was no evidence of improved diabetes control by support from the spouse or by family and friends.[92]

A further systematic review examined the role of interventions involving the family in the treatment of adult patients with chronic physical diseases, on the assumption that families can be highly influential on an individual's self-care. Interventions were either psychoeducational, about the disease and its treatments, or focused on improving relationships within the family, so as to facilitate problem solving and reduce illness related stress. The comparison was groups undergoing usual care, which in some cases included additional education or counselling at the request of the patient. In 52 RCTs, there was considerable heterogeneity in the interventions, disease types studied, outcomes and time frames. There was some evidence of benefit for family based interventions: mean overall effect sizes were 0.32 (95% CI 0.18 to 0.45) for the patients' physical health, 0.28 (0.12 to 0.43) for the patients' mental health, and 0.35 (0.05 to 0.66) for the family members' health.[45]

A systematic review of interventions to support caregivers amongst families of those with terminal illness showed some evidence of benefit of psychosocial interventions.[53] However, trials had high heterogeneity in terms of their design and outcomes and no meta-analysis was performed. Only one of five trials demonstrated no benefit, and the others reported improved carer perceptions of their situation or improved quality of life.

One systematic review examined non-pharmacological interventions for the caregivers of stroke survivors focussing on what kinds of services could help. Eight RCTs were identified, with substantial variation in their design and statistical heterogeneity prevented pooling of results. Interventions included information provision, training for caring, others were psychosocial, aiming to raise resilience and promote well-being in the carers. Two studies using a support and information intervention provided data on the Caregivers Strain Index: pooling these gave a SMD -0.29 (95% CI -0.86 to 0.27) for the intervention, but with substantial heterogeneity ($I2=61\%$). Data were pooled from two other studies on the outcome stress/burden of caregivers, intervention versus comparator SMD was 0.01 (-0.34 to 0.36) with no significant heterogeneity ($I2=0\%$).[59]

We found seven lower quality reviews in the following disease areas: CVD, diabetes and combined chronic diseases including CVD and cancer.[116 136 148 157 159 163 166] In hypertension, a community health worker did not improve blood pressure (BP) control when compared with usual

care. Interventions aimed at couples had small significant effects on patient depressive symptoms on a number of chronic diseases including cancer and CVD.

In conclusion, community support and family involvement are opportunities to strengthen knowledge, self-efficacy and build capacity to deliver self-care across a range of chronic diseases. In some settings, these may offer the main route to providing structured support for self-care, where other forms of health delivery are lacking. Anecdotal evidence suggests that chronic disease programmes involving the community are widespread. However, there is little randomised trial evidence on the effectiveness of such interventions.

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
1.1	Community interventions can complement primary health care. Structured training for community workers should be undertaken to aid the detection and on-going management for NCDs.	Weak	Very low
Research recommendations			
R1	Research is needed to identify pragmatic community based interventions for self-care of NCDs in LMIC. Community programmes should be evaluated for their coverage, generalisability, impact and cost effectiveness.		

GRADE tables for question 1 are presented in Appendix 4.

The evidence-to-recommendation table is presented in Appendix 5.

Question 2: In patients with non-communicable diseases do lay led self-management patient programmes improve outcomes?

Definition: Lay led self-management education programmes are highly structured programmes for people with NCDs which are primarily educational, and address self-care of the disease with the majority of course content delivered by lay individuals.

Summary of evidence

Three systematic reviews were identified which examined trials relating to lay led self-management programmes in self-care.26 39 65 Within these, one trial was performed within LMIC.

One systematic review examined evidence of one-to-one volunteer support among women with breast cancer, compared with usual care, or cancer nurse support, or psychopharmacological treatment. The review presented limited, poor quality evidence to show any benefit of such peer support programmes among those with breast cancer.65

In a systematic review of peer support telephone calls for patients with a variety of health problems meta-analysis was not performed. Peer support telephone calls were found to improve uptake of mammograms in women > 40 years. For myocardial infarction patients, peer support telephone calls were found to improve diet at six months (54% intervention versus 44% usual care (p = 0.03)) but no differences in outcomes were found in patients with poorly controlled diabetes.26

One review examined the evidence on lay led self-management patient programmes across a range of disease conditions. This directly aimed to evaluate the benefits of structured, manualized, lay led self-management programmes among 17 trials randomising [7,442] study participants with long-term health conditions, including arthritis, diabetes, hypertension, chronic pain and other diagnoses. In these trials the comparison was usual care which typically incorporated standard education materials and in some trials, the offer of the lay led course once the trial was completed. The follow-up period for most of these studies was three to six months. Improvement in terms of pain, disability, fatigue and exercise were small and not clinically important.[39]

In conclusion, the use of lay (peer) led self-management disease programmes has grown based on utilising the knowledge and commitment of individuals who have chronic disease to educate and support others with chronic disease. Lay led programmes may help support individuals to take more responsibility for their own health. In regions with highly developed health care systems, lay led programmes may support a shift towards a more partnership model of health care; in areas with little health care coverage they may provide an essential basis for self-care.

We found no lower quality reviews on this topic.

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
2.1	The use of highly structured lay led self-management patient programmes for self-care in NCDs is not recommended at the present time for LMIC.	Weak	Very low
Research recommendations			
R2	Research is needed to evaluate lay led self-management programmes in LMIC, ideally with identification of the active components of such programmes and their feasibility in low resource settings.		

GRADE tables for question 2 are presented in Appendix 4.

The evidence-to-recommendation table is presented in Appendix 5.

Question 3: In patients with non-communicable diseases do online resources for self-care improve outcomes?

Definition: Online resources for self-care include: health information, interactive health communication applications (web based information packages that can combine health information with at least one component of support, decision support or behaviour change support).

Summary of evidence

We obtained data from three systematic reviews evaluating evidence on online resources in self-care. One focused on diabetes[84] and the other two included studies of a range of chronic diseases including CVD, diabetes and respiratory (chronic obstructive pulmonary) disease.[35 73]

One review examined the evidence for web based interventions in the management of type 2 diabetes. The evidence was generally poor quality and the authors reported that goal-setting, personalised coaching, interactive feedback and online peer support groups were some of the successful approaches which were applied in e-interventions to manage type 2 diabetes. There was no pooled analysis and the effects on clinically relevant outcomes were limited.[84]

One review examined the evidence on interactive health communications applications (IHCAs) which are web based information packages for patients that combine health information with at least one of social support, decision support, or behaviour change support. Interventions could be a game or information website. IHCAs had a significant positive effect on knowledge (SMD 0.46, 95% CI 0.22 to 0.69), social support (SMD 0.35, 0.18 to 0.52) and clinical outcomes (SMD 0.18, 0.01 to 0.35). Results suggest that IHCAs might have a positive effect on self-efficacy (SMD 0.24, 0.00 to 0.48). It was not possible to determine the effects on emotional or economic outcomes and there was considerable heterogeneity amongst outcomes.[73]

A systematic review of e-health (monitoring, treatment instructions, self-management training and general information and communication between patient and caregiver), or e-health in addition to usual care found most studies showed small to moderate positive effects on health outcomes. Due to the different study populations that were included and differences in the way that e-health interventions were delivered (instead of usual care or in addition to usual care), results could not be combined and meta-analysis was not performed. However, not all outcomes improved, and in some measures, comparable effect sizes were seen in the intervention and control group.[35]

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In conclusion, accessing health information online has become widespread in developed regions. Health care providers may provide medical information, but content provided by pharmaceutical companies and businesses promoting herbal or complementary preparations is also commonly accessed. Internet accessibility, although extensive, is not uniform worldwide, with some regions having low access and some regions experiencing government control over access. Literacy and language barriers make internet resources inaccessible to some groups.

We found ten reviews deemed to be lower quality.[103 104 109 117 121 131 149 158 170 176] Within these, cardiovascular disease home based secondary programmes and remote patient monitoring seemed to improve quality of life and reduced hospitalisations. One review of telemonitoring in heart failure reported modest improvements in quality of life and decreased hospitalisations. In hypertension, computer based interventions had no effects. In diabetes, web based educational tools showed small improvements in clinically relevant outcomes and enhanced patient-provider communication. There was some evidence that a simple pocket sized insulin dosage computer reduces hypoglycaemic events and insulin doses.

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
3.1	Health care organisations should provide access to user-friendly, valid and reliable online information targeted at NCDs and their management. Online resources could provide some benefit.	Weak	Very low
Research recommendations			
R3	Research is needed to evaluate interactive health care web resources, particularly in LMIC settings.		

GRADE tables for question 3 are presented in Appendix 4.

The evidence-to-recommendation table is presented in Appendix 5.

Question 4: In patients with non-communicable diseases do self-monitoring devices improve outcomes?

Definition: On-going management of NCDs often involves monitoring of a biochemical or physical measure (e.g., blood pressure, blood glucose, peak flow etc.). Whilst these measures can be undertaken in the clinic setting they may be self-monitored in the home setting by the patient or within the community and the results communicated to a health professional for subsequent management.

Summary of evidence

We found 22 systematic reviews on oral anticoagulation, heart failure, hypertension, diabetes (types 1 and 2) and asthma.[1 8 11 14 16 19-22 37 40 43 47 49 51 67 78 81 85 87 94 98] We found no reviews on self-monitoring in cancer.

A review on self-monitoring and self-management of oral antico-agulation reported the combined interventions produced significant clinical benefits. Self-monitoring alone (7 trials, 1027 participants) significantly reduced major haemorrhages (RR 0.56. 0.35 to 0.91) but not thromboembolic events (RR 0.57, 0.32 to 1.00), nor mortality (RR 0.84, 0.50 to 1.41).[40] The self-management studies are reviewed under Question 6.

A systematic review of RCTs that looked at multidisciplinary interventions among participants with heart failure, some of which included home monitoring, was identified. Overall, multidisciplinary interventions reduced all-cause admission (RR 0.87, 95% CI 0.79 to 0.95). All-cause mortality was also reduced (RR 0.79, 0.69 to 0.92) and heart failure admission (RR 0.70, 0.61 to 0.81). In relation to self-monitoring, data could not be isolated from the overall data presented in the review.[49]

A review of 25 trials of self-monitoring in hypertension, compared with usual care found systolic BP and diastolic BP were significantly reduced with self-monitoring: WMD –3.82 mmHg (95% CI, –5.61 to –2.03) for systolic and –1.45 mmHg (–1.95 to –0.94) for diastolic. The likelihood of meeting BP targets was increased (RR 1.09, 95% CI 1.02 to 1.16). This substantial evidence indicates that at a population level, self-monitoring in hypertension may give rise to small but clinically important reductions in blood pressure.[11]

One review looked at the role of continuous blood glucose monitoring via a wire-type glucose sensor implanted in the subcutaneous tissue to monitor the glucose concentration of interstitial fluid in people with diabetes compared with conventional self-monitoring. Comparing the continuous monitor group with the standard self-monitoring of blood glucose, the mean difference in HbA1c was -0.30% (95% CI -0.43 to -0.17). Again, the difference is statistically significant but not clinically meaningful, although in this case the direction of effect supported the use of continuous monitors rather than standard self-monitoring.[78]

A pooled analysis of individual patient data from six randomised trials of self-monitoring of blood glucose in people with non-insulin treated type 2 diabetes found at six months follow-up, mean HbA1c was reduced in the self-monitoring group compared with the usual care group -2.7 (95% CI -3.9 to -1.6). At one year, it was -2.5 (-4.1 to -0.9). This high quality evidence showed that self-monitoring of blood glucose levels among patients with type 2 diabetes produces a statistically significant but not clinically meaningful reduction in HbA1c.[37]

We found fourteen lower quality reviews in the following areas: CVD (10), diabetes (4).[102 119 123 129 134 139 150 161 167 168 179 181 182 184]

In conclusion, self-monitoring of symptoms, body weight or other health indicators and communication of this information to a health care professional for medical guidance is currently undertaken across a wide variety of NCDs. Several devices to support this have been marketed, including blood pressure monitors, blood or urine glucose monitors and oral anticoagulation monitors. Self-monitoring offers the opportunity for more frequent data collection about an individual's condition, potentially more convenient to the individual than visits to a health centre and at lower cost overall, particularly if there is a large distance to a clinical facility.

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
4.1	Self-measurement to monitor blood pressure is recommended for the management of hypertension in appropriate patients where the affordability of the technology has been established.	Strong	Low
4.2	Self-monitoring of blood coagulation is recommended for appropriate patients treated with oral anticoagulation agents, where the affordability of the technology has been established.	Weak	Moderate
4.3	The use of self-monitoring of blood glucose in the management of patients with type 2 diabetes not on insulin is not recommended at the present time because there is insufficient evidence to support such a recommendation.	Weak	Moderate
4.4	People with type 1 and type 2 diabetes on insulin should be offered self-monitoring of blood glucose based on individual clinical need.	Weak	Low
Research recommendations			
R4	Research is needed to evaluate the impact of self-monitoring, including assessment of the cost-effectiveness in LMIC.		

GRADE tables for question 4 are presented in Appendix 4.

The evidence-to-recommendation tables are presented in Appendix 5.

Question 5: In patients with non-communicable diseases do mobile telephone and/or telemonitoring interventions targeted at self-care improve outcomes?

Definition: Telemonitoring involves remotely monitoring patients who are not in the same location as the health care provider. Monitoring devices will transmit information on symptoms and/or vital signs via the telephone to a remote monitoring service provider and/or to their

health care provider. Telemedicine is a broader concept that includes patient consultations using telecommunications.

Summary of evidence

We extracted data from 14 systematic reviews on CVD (heart failure, hypertension and myocardial infarction), diabetes and respiratory disease (asthma and COPD). Among these, one trial was performed in a low or middle income country.[1 4 9 26 27 36 49 55 61 69 70 80 85 93] We found no reviews on mobile telephone or telemonitoring interventions among participants with cancer. One trial was performed in LMIC.

A review of multidisciplinary interventions among participants with chronic heart failure, some of which included telecare, found all-cause hospital admissions (RR 0.87, 95% CI 0.79 to 0.95), mortality (RR 0.79, 0.69 to 0.92) and heart failure admission (RR 0.70, 0.61 to 0.81) were all reduced. But it was difficult to identify the role of telemonitoring within these and the comparison groups were poorly described.[49]

One review, of 25 RCTs in chronic heart failure patients, reviewed structured telephone support (using simple technology) and telemonitoring (digital/ broadband/satellite/wireless or Bluetooth transmission data). Telemonitoring reduced all-cause mortality (RR 0.66, 95% CI 0.54 to 0.81) and structured telephone support also reported a nonsignificant reduction in mortality (RR 0.88, 0.76 to 1.01). Both interventions reduced CHF related hospitalisations: telephone support (RR 0.77, 0.68 to 0.87) and telemonitoring (RR 0.79, 0.67 to 0.94). Several studies reported improvements in quality of life as well as reduced health care costs and acceptability to patients.[55]

A systematic review of 22 trials of home BP monitoring compared with clinic monitoring included five trials of telemonitoring. Overall results showed an improvement for systolic BP for home monitoring (-2.63mmHg, 95% CI -4.24 to -1.02) and diastolic BP (-1.68mmHg, -2.58 to -0.79). Reductions in home BP monitoring-based therapy were greater when telemonitoring was used (five trials) (SMD -3.20 mmHg, -4.66 to -1.73) compared to when telemonitoring was not used (17 trials) (SMD -1.26 mmHg, -2.20 to -0.31) for systolic BP but not for diastolic BP.[1]

A review of the role of telemedicine compared with usual care among participants with type 1, type 2 or gestational diabetes on HbA1c control reported two trials used a mobile phone, most transmitted blood glucose data, self-management information and insulin dose, two transmitted blood glucose data and self-management information and one only transmitted blood glucose data. Half the studies used advanced signal processing and six displayed blood glucose data. Among nine RCTs there was no significant benefit of telemedicine for HbA1c (WMD -0.11, 95% CI –0.27 to 0.04).[36]

A review of mobile phone interventions among individuals with type 1 or 2 diabetes reported most of the 22 included trials used a mobile phone short message service SMS to deliver blood glucose test results and self-management information among participants with type 1 or type 2 diabetes. The overall result was a small reduction in HbA1c in the intervention group (SMD -0.51, 95% CI -0.69 to -0.33) over a median of 6 months follow-up. The effect of mobile phone intervention did not significantly differ by other participant characteristics or intervention strategies.[61]

Six trials were included in a review of interventions incorporating tele-consultation, videoconferencing or videoconferencing combined with tele-consultation in the care of individuals with diabetes. There was little evidence of benefit of these interventions: HbA1c was not reduced with tele-consultation compared with usual care (WMD 0.03, 95% CI -0.31 to 0.24). There was no evidence of heterogeneity. The study also looked at patient satisfaction and other non-clinical outcomes. The benefits of videoconferencing were mainly related to its effects on socioeconomic factors such as education and cost reduction, but also on monitoring disease. Additionally, videoconferencing seemed to maintain quality of care while producing cost savings.[93]

A review of 24 studies of mhealth (mobile health technologies) interventions in type 1 and 2 diabetes reported that studies were inconsistent, often of poor quality, which negated the evidence for effectiveness.[4]

A review of 21 studies looked at telecare interventions among participants with asthma compared with usual care or any other form of control. A range of technologies were included: telephone (n = 9); video conferencing (n = 2); internet (n = 2); other networked communications (n= 6); Short Messaging Service (text) (n = 1); or a combination of text and internet (n = 1). Over a 12-month period, telecare resulted in a non-significant increase in the odds of emergency department visits (OR 1.16, 95% CI 0.52 to 2.58) but, over the same period led to a significant reduction in hospitalisations (OR 0.21, 0.07 to 0.61). The effect size was more marked in those with more severe asthma: those managed predominantly in secondary care settings.[69]

Telemonitoring in chronic obstructive pulmonary disease was analysed in a review including six studies, two of which used control groups and two used a before and after design. Four of six studies reported a reduction in hospital admission, but only one of these was a RCT.[9]

In a review of telehealthcare among participants with COPD the interventions were: video or telephone links with health care professionals; internet based telecommunication with health care professionals; wired and wireless telemetry for telemonitoring of spirometry (FEV1/FVC), respiratory rate, BP and O2 saturations. In two trials

telehealthcare was associated with a non-significant increase in quality of life (MD -6.57, 95% CI -13.62 to 0.48). Telehealthcare also showed significant reductions in emergency department attendances over a 12-month period (OR 0.27, 0.11 to 0.66) and admissions to hospital (OR 0.46, 0.33 to 0.65). There was no significant difference in deaths over the same period (OR 1.05, 0.63 to 1.75).[70]

In a review of peer support telephone calls for patients with a variety of health problems meta-analysis was not performed. Peer support telephone calls were found to improve uptake of mammograms in women > 40 years. For myocardial infarction patients peer support telephone calls were found to improve diet at six months (54% intervention versus 44% usual care, p = 0.03), but no differences in outcomes were found in patients with poorly controlled diabetes.[26]

Evidence from 22 lower quality reviews suggested home based interventions, including telephone based interventions, improved quality of life in patients with cardiovascular disease. [106 114 123 127 128 137 140 141 144 145 149-152 156 158 162 169 171 173 174 183] In stroke, one review reported home based telerehabilitation showed promising results in improving the health of stroke patients. In COPD, telehealth (telemonitoring and telephone support) reduced rates of hospitalisation and emergency department visits. Eight reviews reported on combined cardiovascular conditions including CVD, heart failure, coronary artery disease, diabetes, hypertension and one review also included respiratory disease (COPD and asthma), which commonly reported improved clinical outcomes. We found no reviews in cancer.

In conclusion the expansion of the mobile telephone (cell phone) networks offers a potential route for communication with health care providers.

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
5.1	The use of telemonitoring for self-care in NCDs is not recommended at the present time, because there is insufficient evidence to support such a recommendation.	Weak	Low
5/2	The use telehealth for self-care in NCDs is not recommended at the present time, because there is insufficient evidence to support such a recommendation.	Weak	Low
Research recommendations			
R5	Research is needed to evaluate telemonitoring and telehealth in LMIC, ideally with identification of the active components of such programmes and their feasibility in low resource settings.		

GRADE tables for question 4 are presented in Appendix 4.

The evidence-to-recommendation tables are presented in Appendix 5.

Question 6: In patients with non-communicable diseases do self-treatment interventions improve outcomes?

Definition: Self-treatment intervention includes self-monitoring and adjustment of dosage of medicines by the individual, based on a pre-specified action plan agreed jointly by a health care practitioner / worker and the patient. A situation can occur in NCD management in which the patient could or will alter the doses and/or frequency of the treatment depending upon the change in the nature severity of symptoms and/or biochemical markers of a disease under the guidance of a professional health care provider (e.g. physician) with treatment recommendation.

Summary of evidence

We extracted data from 12 systematic reviews evaluating self-treatment intervention programmes in cardiovascular disease (oral anticoagulation, chronic heart failure), diabetes, respiratory disease (COPD and asthma), and combined chronic diseases. [8 20 22 30 34 40 41 58 71 79 82 96] We found no reviews of self-care treatment interventions in cancer.

Self-management of oral anticoagulation, comprised of self-monitoring and self- treatment, when compared with usual care showed significant reductions in thromboembolic events (RR 0.47, 95% CI 0.31 to 0.70) and all-cause mortality (RR 0.55, 0.36 to 0.84); there was no evidence of effect on major haemorrhage (RR 1.12, 0.78 to 1.61).[40]

In one review, of patients with heart failure, the self-treatment intervention groups involved patients who were educated about early recognition of signs and symptoms of heart failure, the importance of pharmacological treatment adherence, daily weighing and changing lifestyle. Comparison was with usual care, or an education package. There was some evidence that self-management reduced all-cause hospital admissions and hospital admissions due to chronic heart failure. However, the trials were heterogeneous and mostly at high risk of bias.[30]

One review looked at studies testing interventions to increase type 2 diabetes patients' adherence to self-management in terms of requirements in diet, exercise, smoking and alcohol. Some studies also looked at blood glucose monitoring. The interventions were classified as either educational or behavioural psychosocial interventions. The analysis showed a 0.36% (95% CI 0.21 to 0.51) improvement in glycaemic control. Most studies were assessed as having a high or unclear risk of bias.[71]

A further review in patients with type 1 or type 2 diabetes looked at disease management programmes which consisted of patient follow-up

that included two or more of the following: patient education, coaching, monitoring, care coordination, and treatment adjustment by a disease manager. Comparison groups were somewhat heterogeneous with varying levels of education and health care worker contact. Among 41 RCTs (over 7,000 participants), disease management programmes resulted in a significant reduction in HbA1c (SMD -0.38, 95% CI -0.47 to -0.29). Programmes in which treatment adjustment was by a disease manager resulted in a greater reduction in HbA1c (SMD -0.60 versus -0.28).[79]

One systematic review examined interventions aiming to improve the delivery of asthma medications by self-management education. Self-management involved self-monitoring by peak expiratory flow or symptoms, together with regular medical review and a written action plan. These self-treatment educational interventions were compared with usual care, which varied between no intervention, education, self-monitoring or regular medical review but not written action plans. Self-management education reduced nocturnal asthma (RR 0.67, 95% CI 0.56 to 0.79); hospitalisations (RR 0.64, 0.50 to 0.82); emergency room visits (RR 0.82, 0.73 to 0.94); unscheduled visits to the doctor (RR 0.68, 0.56 to 0.81). Measures of lung function were little changed: SMD for peak flow was 0.18, 95% CI 0.07 to 0.29 and SMD for FEV1 0.10, -0.02 to 0.22. The trials included in this review were mostly at a high risk of bias.[41]

A further review of studies comparing asthma self-management using a written action plan based on peak flow expiratory flow with a plan based on symptoms showed no significant effects on emergency room visits, hospitalisation and days off work. This review also analysed three studies comparing the asthma self-management with self-adjustment of medications according to an individualised written action plan to medication adjustment by a doctor. For intervention versus control peak flow was improved (SMD 0.16, 95% CI 0.01 to 0.31) as well as FEV1 (SMD 0.10, -0.05 to 0.25). The evidence, based on studies at high or unclear risk of bias, suggests optimisation of asthma control can be achieved equally as well by self-adjustment with the aid of a written action plan or by regular medical review.[82]

A review of COPD self-management education interventions found hospital admissions were reduced (OR 0.64, 95% CI 0.47 to 0.89), which translates, in patients with a moderate risk of exacerbation into a number needed to treat (NNT) of 10 (6 to 35) and a NNT of 24 (16 to 80) for patients at low risk.[34]

In a systematic review of actions plans with minimal or no education for COPD, the action plans gave guidance on self-initiated interventions including medication modification. The use of action plans did not reduce hospitalisation, emergency room visits and increased the use

of oral corticosteroids over 12 months (MD 0.74, 95% CI 0.14 to 1.35). Antibiotic use over 12 months was also increased (MD 0.78, -0.24 to 1.79). There was also no significant difference in knowledge about self-management for exacerbations.[96]

There were five lower quality reviews.[137 138 146 147 167] In oral anticoagulation self-management results were consistent with other reviews. In heart failure, one review reported self-management interventions led to increased adherence to prescribed medical advice but with no improvement in functional capacity. In type 2 diabetes, there was low quality evidence that tracking systems for medication use may improve HbA1c.

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
6.1	Self-monitoring of blood coagulation and self-adjustment of dosage in patients receiving oral anticoagulation agents is recommended if affordable and according to an agreed action plan with a health professional.	Weak	Moderate
6.2	Self-monitoring in asthma and COPD and self-adjustment of dosage is recommended according to an agreed action plan with a health professional.	Weak	Very low
6.3	Self-adjustment of diuretics based on body weight monitoring in heart failure is not recommended at the present time.	Weak	Very low
6.4	Self-monitoring of blood glucose and self-adjustment of insulin dosage is recommended in type 1 diabetes according to an agreed action plan with a health professional.	Weak	Low
Research recommendations			
R6	Research is needed to establish a consistent evidence base upon which valid recommendations can be made for self-monitoring and self-adjustment of treatments, particularly in LMIC. The research should evaluate risks and benefits, outcomes, cost and quality of life and also acceptability and potential barriers.		

GRADE tables for question 6 are presented in Appendix 4.

The evidence-to-recommendation tables are presented in Appendix 5.

Question 7: In patients with non-communicable diseases do self-care education/information programmes improve outcomes?

Definition: Education is the process of receiving or giving systematic instruction about a specific aspect of disease whilst information is the knowledge communicated about a particular aspect of a disease.

We extracted data from 35 systematic reviews in cardiovascular disease (coronary heart disease, hypertension and stroke), diabetes,

respiratory disease (asthma and COPD), cancer and combined chronic diseases.[2 5-7 10 15 24 29 31-34 38 42-44 50 52 54 57 60 62-64 68 74 75 77 88-90 94 97 99 100]

One review of the impact of psychoeducation programmes among people with coronary heart disease comprised of interventions delivered by trained health care professional, group or individual based, conducted in the home or community or as part of a cardiac rehabilitation programme. The comparison was with exercise only, standard cardiac rehabilitation or medical care. Psychoeducational interventions produced a significant positive effect on physical activity levels over the medium term (six to 12 months) when compared with exercise and risk factor education (SMD 0.62, 95% CI 0.30 to 0.94). There was little change in smoking and dietary behaviour. The studies were mostly at high or unclear risk of bias.[2]

A review of psychosocial interventions for smoking cessation in patients with coronary heart disease found that there was a positive effect on abstinence (OR 1.66, 95% CI 1.25 to 2.22). The interventions were either stand-alone smoking cessation interventions or ones which were included in more comprehensive rehabilitation programmes. They consisted of behavioural therapeutic interventions, phone support and self-help material. Comparison was with usual care, which varied between studies. Long-term data on whether quitting smoking was maintained were not available.[5]

A systematic review investigated a range of psychological interventions for coronary heart disease. There was little evidence that psychological interventions reduced mortality (RR 0.89, 95% CI 0.75 to 1.05). Psychological interventions in a smaller number of studies reporting cardiac mortality showed a small positive effect (RR 0.80, 0.64 to 1.00). Psychological interventions resulted in small to moderate improvements in depression (SMD -0.21, 95% CI -0.35 to -0.08) and anxiety (SMD -0.25, -0.48 to -0.03).[99]

One systematic review focussed on the effects of information provision among stroke patients (and their caregivers), including 21 RCTs of which nine included active information delivery interventions (lectures, home visits, or multi-component interventions) and 12 included only passive information provision (leaflets, in some cases tailored to the participant).[38] Overall the risk of bias was moderately high and the high heterogeneity prevented pooling thus limiting the ability to draw conclusions. From subgroups of studies, there was mixed evidence as to whether anxiety or depression was reduced by information provision, and no evidence of reduction in mortality.

In a review of 17 studies of the evidence on interventions to increase self-efficacy among participants after stroke, which included four RCTs, the interventions were highly varied, and meta-analysis was

not performed. Four self-efficacy interventions were identified; the evidence for the effects of these interventions was inconclusive.[57]

A review of interventions to improve the control of BP among participants with hypertension included a range of interventions, some of which were educational interventions directed towards the patient. Trials were heterogeneous but appeared unlikely to be associated with large net reductions in BP by themselves (WMD systolic BP -0.57 mmHg, 95% CI -1.22 to 0.08), and diastolic BP (0.46 mmHg, 0.07 to 0.86).[134]

A review of dietary interventions in hypertensive patients showed that body weight and BP were reduced in patients assigned to weight loss diets as compared to controls. The interventions were dietary education and direction, such as advising caloric restrictions or reduction in fat intake, and were compared with no interventions aiming to reduce body weight. Comparing intervention with control, body weight was reduced (WMD -3.98kg, 95% CI -4.79 to -3.17) over 6 months to three years. In addition, there was evidence that BP was reduced (WMD -4.5 mmHg, -7.2 to -1.8 mm Hg) and diastolic BP (WMD -3.2 mmHg, -4.8 to -1.5 mmHg).[89]

Systematic reviews of type 2 diabetes education or information programmes demonstrated variable results and reported only modest reductions in clinically relevant outcomes. Most of the evidence available for these reviews were derived from studies at high risk of bias. Group based educational interventions compared with usual care or remaining on the waiting list for the intervention, delivered modest reductions in HbA1c and reduced the need for diabetes medications. At four to six months follow-up, HbA1c was reduced by -1.35 (95% CI -1.93 to -0.78). At 12 to 14 months follow-up, this reduction was -0.82 (-0.99 to -0.65). There was also evidence of reduced need for diabetes medication, based on five RCTs with 654 participants.[29]

There was limited, inconsistent evidence that education on foot care could reduce foot ulceration or amputation. This systematic review examined 12 studies, of which three studies described the effect of foot care education compared with usual care, two studies examined the effect of tailored foot care educational needs compared with no intervention and seven studies described the effect of intensive versus brief educational interventions. The studies were too heterogeneous to allow meta-analysis, and the results were inconsistent and overall too limited to draw conclusions from.[31]

A second review evaluating face-to-face education showed no improvement; however, in a subgroup analysis of patients with higher baseline HbA1c levels there was some evidence of modest benefit. In studies comparing individual face-to-face education to usual care,

individual education did not significantly improve HBA1c (WMD -0.08, 95% CI -0.25 to 0.08) over 12 to 18 months. In this same review, a comparison of individual education with group based education detected no difference in the effects of these interventions.[33]

Evidence for educational interventions among people with diabetic kidney disease was limited and inconclusive. The systematic review identified only two trials, with low to moderate methodological quality, and more data are needed.[60]

There was limited and inconclusive evidence on the effect of educational interventions focussed on weight loss among type 2 diabetes patients: only modest weight loss was achieved, and comparison groups also often achieved weight loss. This systematic review identified 22 RCTs of weight loss or weight control interventions, via dietary, physical activity or behavioural strategies, compared with either usual care, similar interventions at lower intensity, or any other weight loss or weight control intervention; thus, the comparisons were not consistent. Among 585 participants, any weight loss intervention led to a reduction WMD -1.72kg (95% CI -3.15 to -0.29) in weight, equivalent to 3.1% of average baseline body weight. Changes in HbA1c usually corresponded to changes in body weight and were not significant when between-group differences were examined.[75]

One review examined the impact of interventions aimed at improving adherence to treatment recommendations. In nine studies HbA1c was improved (WMD -0.49, 95% CI -0.73 to -0.25). Most of the studies examined by the systematic reviews on this topic were at high or unclear risk of bias and sample sizes were frequently small.[94]

A review of limited asthma education found it did not significantly reduce hospitalisations (WMD -0.03, 95% CI -0.09 to 0.03) but did reduce emergency department visits (WMD -2.76, -4.34 to -1.18).[42] A further review examined the evidence for mite control measures among people with house dust mite sensitive asthma. Thirty-seven trials assessed physical methods including mattress encasings (26 trials). Ten trials examined chemical methods and eight trials involved a combination of both. Compared with usual care, there was little evidence of benefit of the interventions. There were no statistically significant differences in the number of patients who improved (RR 1.01, 95% CI 0.80 to 1.27).[44]

In a review of trials of breathing exercises for participants with asthma five trials compared breathing retraining with no active control and two with asthma education control groups. Comparing intervention with control, rescue bronchodilator use was lower WMD -5.82 (95% CI -8.70 to -2.94), FEV1 was no different WMD -0.19 (-0.70 to 0.31) and daily peak flow improved WMD 72 Litres (30.15 to 113.85).

Overall, benefits of breathing exercises were found in isolated outcome measures across single studies.[50]

In a review of studies of relaxation therapies among participants with asthma, the interventions included progressive relaxation, hypnotherapy or autogenic training. Comparison group interventions varied widely from assertiveness training, sitting quietly, placebo relaxation method and listening to relaxing music. Two of five RCTs reported benefits of progressive muscle relaxation or mental and muscular relaxation. One RCT investigating hypnotherapy, one of autogenic training, and two of biofeedback techniques revealed no therapeutic effects. Overall, the methodological quality of the studies was poor. There was no evidence of benefit of psychological interventions among asthma patients from a review of 12 RCTs with 384 participants, which compared psychological interventions with some form of control intervention. No meta-analysis could be performed due to the diversity of interventions and the outcomes assessed and overall there was no evidence to show benefit of psychological interventions.[54]

A systematic review of the role of COPD-specific patient education compared with usual care, the intervention amongst 10 RCTs included various education delivery methods and settings. No meta-analysis was possible due to study heterogeneity. Self-management education tended to reduce hospital admissions, and tended to decrease costs associated with GP visits, but overall, there was insufficient evidence that increased knowledge leads to better self-care in COPD.[7] A further review of self-management education interventions for COPD patients found that the probability of hospital admissions was reduced with these interventions (OR 0.64, 95% CI 0.47 to 0.89), which translated into a NNT of 10 (6 to 35) for patients with a moderate risk of exacerbation, and a NNT of 24 (16 to 80) for patients with a low risk of exacerbation.[34]

A systematic review of the provision of pain management of cancer patients was identified. Six studies gave estimates suggesting reduced pain in the intervention group: pain interference: (SMD 0.02, 95% CI -0.11 to 0.16); usual/average pain: (SMD 0.43, 0.13 to 0.74); and five studies for worst pain: (SMD 0.22, -0.20 to 0.64). It was not possible to isolate the results for studies targeting family/community from patients alone.[24]

Another review of educational interventions on cancer pain identified four RCTs using information, behavioural instructions via verbal, written or recorded audio-visual messages. Outcomes assessed included pain and pain intensity, quality of life scores such as functional status, perceived pain control, well-being and anxiety. The comparator was either usual care or a less intensive educational intervention such as a leaflet being given. These studies were heterogeneous in participant group, the type and delivery method of the intervention, outcome

assessment and all were at moderate risk of bias. There was very little consistent evidence of benefit of the educational interventions on pain or quality of life scores.[62]

A review of psychosocial interventions to reduce cancer pain, which pooled data from 37 RCTs, reported reductions in pain and interference by pain among those receiving the interventions. Interventions comprised skills training, cognitive-behavioural therapy, relaxation, hypnosis, and conditioning cues; the comparator was usually usual care. Study quality was typically low. For pain severity, the weighted average effect was 0.34 (95% CI, 0.23 to 0.46) and relative risk for pain interference was 0.40 (0.21 to 0.60) among the intervention compared with usual care.[88]

Limited, inconsistent evidence on self-management education among breast cancer patients suggested no benefit on quality of life or anxiety.[74]

A review of pelvic floor muscle training among men who have had radical prostatectomy, reported that one trial of 300 men found that training improved continence rates; men receiving biofeedback-enhanced training were more likely to achieve continence or have no continual leakage than those with no training within one to two months, but that the relative benefit increase was no longer significant after three to four months. Biofeedback enhanced pelvic floor muscle training was comparable to written or verbal pelvic floor muscle training instruction. Extracorporeal magnetic innervation and electrical stimulation were found to be initially (within one to two months) more effective than pelvic floor muscle training in one trial, but there were no significant differences between groups at three or more months.[64]

In chronic diseases, general advice and education interventions had limited effects. One review looked at studies of single risk factor interventions to promote physical activity among patients with chronic diseases, compared with usual care. Three trials were identified: one looked at general practitioners' prescription; counselling by practice nurses; and distribution of an education leaflet. A second examined advice about becoming more active and an eight week follow-up including visits with the health care provider and two booster telephone calls from a counsellor in physical activity. The third looked at material and medical advice encouraging more physical activity and to manage their hypertension better, supplemented with a self-help booklet. Two studies reported that the interventions evaluated had no effect on level of physical activity. One study reported a short-term increase in physical activity levels with use of an intensive intervention that was based on the theory of planned behaviour and integrated nurses into the general practitioner counselling process.[52]

A further review investigated self-management education programmes across a range of chronic diseases. Interventions involving face-to-face contact were associated with better outcomes. No other trial characteristics were associated with improved outcomes. Among diabetic patients, comparing education with usual care reduced HbA1c by 0.45% (95% CI 0.17 to 0.74), reduced systolic BP by 0.20mmHg (0.01 to 0.39), but did not significantly reduce diastolic BP (0.10 mmHG, -0.06 to 0.26 mmHg). Among participants with asthma, comparing education with usual care reduced asthma attacks: log rate ratio was 0.59 (95% CI 0.35-0.83). In a meta-regression, interventions involving face-to-face contact were associated with better outcomes; no other intervention characteristics were associated with improved outcomes.[97]

Thirty-six lower quality reviews were found in the following disease areas: cardiovascular disease, diabetes, respiratory disease and cancer.[101 105 107-113 115 118 120 122 124-126 129 130 132 133 135 142 143 153 155 157 160 164 165 175 176 178 180 185-187]

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
7.1	Group education programmes, rather than individual education, may offer a cost effective strategy to deliver education in LMIC.	Weak	Very low
Research recommendations			
	None		

GRADE tables for question 7 are presented in Appendix 4.

The evidence-to-recommendation table is presented in Appendix 5.

Question 8: In patients with non-communicable diseases do self-care rehabilitation programmes improve outcomes?

Definition: Rehabilitation therapy aims to improve function that has been lost or diminished by disease. Rehabilitation programmes may incorporate exercise and/or information after an event such as a myocardial infarction.

Rehabilitation is used among patients after interventions such as coronary angioplasty, heart surgery, or after stroke, in patients with chronic heart failure or respiratory problems. It consists of exercise training, usually combined with counselling and advice. The aim is to reduce the risk of future problems, help patients understand their condition, and help patients make lifestyle changes to support better health. Where the patient undertakes exercise by themself, this is self-care. As in all areas of self-care, the model is that health care

professionals deliver the education and training to the individual, and the individual may then take on more responsibility and autonomously perform the intervention. In practice, the ability of individuals to self-care during rehabilitation will vary and it will not be appropriate for all individuals. It is also essential that the programme be performed in the context of advice and support from health care professionals. The presented reviews examine various facets of these interventions.

Summary of evidence

We identified 13 reviews. [3 12 13 18 23 25 28 48 56 72 83 91 95]

A review of home based rehabilitation versus centre based rehabilitation reported across the 12 included trials. The components of the interventions varied. Home based was not better than centre based for systolic BP (WMD 0.58mmHg, 95% CI -3.29 to 4.44) and for total cholesterol (WMD -0.13mmol/L, -0.31 to 0.05). There was no difference in mortality for home based versus centre based (RR 1.31, 0.65 to 2.66).[25]

In terms of exercise based interventions either alone or as a component of comprehensive cardiac rehabilitation, there was no significant difference in pooled mortality between groups in the 13 trials with less than one year follow-up.[28] There was a non-significant a reduction in pooled mortality in the four trials with more than one year follow-up (RR 0.88, 95% CI 0.73 to 1.07).

Home based exercise programmes comprising aerobic exercise with or without resistance exercise compared to usual care or usual activity among individuals with chronic heart failure,18 led to an increased six minute walking distance WMD 41 metres (95% CI 19 to 63) and peak VO2 WMD 2.71 ml/kg/min (0.7 to 4.7). Home based exercise did not significantly increase hospitalisation rates (OR 0.75, 95% CI 0.19 to 2.92) more than usual activity.

A review of the efficacy of physical fitness training for patients after stroke compared with no intervention, a non-exercise intervention or usual care reported trials were heterogeneous in outcomes, and in quality, and data pooling was difficult. There were no data on mortality or hospitalizations. Training involving walking had a positive effect with the mean maximum walking speed improving by 8.66 metres per minute, (95% CI 2.98 to 14.34). The effects were retained at the end of follow-up. Resistance training did not report sufficient data to assess its effects whilst the effects of physical training on mortality and disability were not clear.[12]

One review looked at the effectiveness of therapy based rehabilitation interventions delivered more than one year after stroke. There was insufficient evidence to form conclusions as to whether interventions

delivered more than one year after stroke could bring benefits to patients after stroke.[3]

One review investigated interventions specifically targeted at upper limb function among participants who had a stroke. Included studies each comprised a therapy programme with several treatment interventions, involving various exercise and task performance. Primary outcomes were activities of daily living and functional movement of the upper limb as primary outcomes. Four RCTs including 166 participants were identified, comparing interventions with usual care or another intervention, and overall there was no evidence of improvement in the primary outcomes. Currently there are not enough data to support the use of home based therapy focussing on upper limb function, and more research is needed.[23]

In a review of 12 RCTs of pulmonary care rehabilitation in COPD, two RCTs and eight studies compared home based rehabilitation to standard care (no pulmonary rehabilitation); three studies compared home based rehabilitation to hospital care and one study made both comparisons. The methodological quality of the included studies was low to moderate and meta-analysis was not performed. Most studies showed increased quality of care and exercise capacity with home based pulmonary care rehabilitation compared with no pulmonary rehabilitation. There was no evidence of differences in outcomes for home based compared with hospital based rehabilitation.[95]

Another recent review of pulmonary care rehabilitation among those with COPD focussed on those recently experiencing a hospital admission for a COPD exacerbation. Nine RCTs compared an intervention delivered in the community with usual care and assessed hospital admissions, as well as mortality, health related quality of life and exercise capacity. There was good evidence from trials at moderate risk of bias that pulmonary care rehabilitation substantially reduced hospital admissions over six months (OR 0.22, 95% CI 0.08 to 0.58), and mortality over a two year period (OR 0.28, 0.10 to 0.84).[83]

One review investigating the role of rehabilitation among participants who had previously completed treatment for cancer (not including the terminally ill or those under hospice care) was identified.[72] The review focussed on whether exercise interventions could improve quality of life. 40 RCTs randomizing 3,694 participants were included, with an exercise intervention such as strength training, resistance training, walking, cycling or yoga. These were compared to usual care or another, non-exercise, intervention, and health related quality of life was assessed using a variety of measures. The trials were heterogeneous in design, exercise intervention and outcome measures and most were at high risk of bias. There was some weak evidence of benefit but the lack of consistency and wide confidence intervals means that

more high quality data are needed before such interventions can be recommended.

There were three lower quality reviews.[143] [154] [177]

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
8.1	Appropriate patients could benefit from being educated on the benefits of cardiac rehabilitation, and can be encouraged to undertake physical activity for rehabilitation in the home setting.	Weak	Very low
8.1	Appropriate patients could benefit from being educated on the benefits of COPD rehabilitation , and encouraged to undertake rehabilitation exercise.	Weak	Very low
Research recommendations			
R8	Research is needed to evaluate the effectiveness of rehabilitation programmes in the home or community across NCDs, particularly in LMIC.		

GRADE tables for question 8 are presented in Appendix 4.

The evidence-to-recommendation tables are presented in Appendix 5.

Question 9: In patients with non-communicable diseases do interventions targeted at adherence improve outcomes?

Definition: Patient adherence has been defined as the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider.

Summary of evidence

Evidence was provided from five systematic reviews, three among participants with diabetes and three in combined chronic diseases.[46] [66] [71] [86] [94]

A review of studies testing interventions to increase the adherence of patients with type 2 diabetes to self-management requirements in diet, exercise, smoking and alcohol reported an improvement in HbA1c of PMD 0.36% (95% CI 0.21 to 0.51). Most studies were assessed as having a high or unclear risk of bias.[71]

Another review examined the impact of interventions aimed at improving adherence to treatment recommendations.[94] In nine studies HbA1c was reduced MD -0.49 (95% CI -0.73 to -0.25).

In a review of the role of reminder packaging in adherence to taking medications, interventions included a reminder system for the day of the week or the time that the medication was to be taken, and formed part of the packaging.[66] Trials of reminders that were separate to the intervention (such as a mailed or SMS reminder) were excluded. Packaging aids were included irrespective of whether the medication required a prescription or not. Trials of over-the-counter medications or vitamin supplements were included. Injected, topical or inhaled medicines, and co-packaged or fixed-dose combinations were included, as long as the packaging included a reminder system. Reminder packaging increased the percentage of pills taken: MD 0.11 (95% CI 0.06 to 0.17), significantly decreased diastolic BP, MD -5.89 mmHg (-6.70 to -5.09). No effect was seen on systolic BP (-1.01 mmHg, -2.22 to 0.20). Reminders significantly reduced HbA1c (MD -0.72, -0.83 to -0.60). In one study, the presence of a reminder packaging aid was preferred by patients with low literacy levels.

A further review reported a broad range of interventions targeted at improving adherence to medications.46 The majority of effective interventions for chronic diseases were complex in nature. They included combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. However, they did not lead to large improvement in adherence. This finding was confirmed by a second review.[86]

In one lower quality review a wide variety of strategies in chronic disease seemingly improve medication adherence, with no single strategy appearing to be the best.[172]

Recommendations

No.	Recommendation	Strength of recommendation	Quality of evidence
9.1	Strategies to improve adherence should form part of self-care for NCDs. Promotion of self-care in NCDs should take into account patients' beliefs and concerns about medicines, and their effects on adherence	Strong	Very low
9.2	No single strategy to improve overall adherence is recommended over another	Weak	Very low
Research recommendations			
R9	Research is needed on interventions to improve adherence, particularly in LMIC.		

GRADE tables for question 9 are presented in Appendix 4.

The evidence-to-recommendation tables are presented in Appendix 5.

See compact disc for full guideline.

IV. Scaling up action against noncommunicable diseases: how much will it cost?

Costing Tool – User Guide

References:
Scaling Up Action against Noncommunicable Diseases: How Much Will It Cost?,
World Health Organization, 2011

Costing Tool – User Guide, World Health Organization, 2012

Summary

This paper describes a new financial planning tool developed by the World Health Organization (WHO) to assist low- and middle income-countries in scaling up a core set of interventions to tackle noncommunicable diseases (NCDs), such as heart disease and stroke, diabetes, cancer and chronic lung disease.

NCDs currently kill 36 million people per year, and the burden continues to escalate, particularly in low- and middle-income countries. These countries often lack resources and capacity to tackle these diseases, and therefore need to adopt an incremental approach as they move to address the gaps in NCD prevention and control.

To prevent disability and death, it will be important to act on two levels - through population-wide measures to reduce exposure to risk factors such as tobacco use, and through interventions targeting individuals who already have NCDs or are at high risk for developing them. A wide range of health interventions is available for both purposes. One challenge is to assess which interventions will bring the most benefit for the lowest cost - in other words, what are the 'best buys'. A further challenge is to assess the cost of their scaled-up implementation.

The WHO tool aims to help countries make that assessment. It is a tool for financial planning (over the period 2011-2025) that can be used to forecast resource needs at national and sub-national levels. The tool can enhance traditional budgeting mechanisms in countries and provide new information to development agencies about the resources needed to tackle the growing burden of NCDs.

The tool has been used to produce a 'price tag' for a combined set of population-based and individual-level 'best buy' NCD interventions that have been identified as priority actions by WHO. The average yearly cost for all low- and middle-income countries is estimated to be US$ 11.4 billion (an overall cost of US$ 170 billion over the period 2011-2025).

The cost per head of population is low. It represents an annual investment of under US$ 1 in low-income countries, US$ 1.50 in lower middle-income countries; and US$ 3 in upper middle-income countries. Expressed as a proportion of current health spending, the cost of implementing such a package amounts to 4% in low-income countries, 2% in lower middle-income countries and less than 1% in upper middle-income countries.

Population-based best buy interventions address tobacco and harmful alcohol use, as well as unhealthy diet and physical inactivity in

low- and middle-income countries. The cost for these approaches US$ 2 billion yearly. In low-income and lower middle-income countries, the median cost per head of population amounts to less than US$ 0.20 per year, while for upper-middle income countries the median value is close to US$ 0.50. These amounts represent less than 1% of total per capita spending on health.

Individual-based best buy interventions are delivered in primary health care settings and include, for example, counselling and drug therapy for persons with or at high risk of cardiovascular disease, plus measures to prevent cervical cancer. For these interventions the cost averages more than US$ 10 billion yearly. Over the scale-up period 2011-2025, the annual cost per head of population falls below US$ 1 in low-income countries, less than US$ 1.50 in lower-middle income countries and averages US$ 2.50 in upper-middle income countries.

Note: It is important to mention that the tool used for this study required a number of data sources and assumptions to be made about which interventions are scaled up, at what pace and to what level of coverage. These may not coincide with a particular country's intentions or health system capacities and not all countries will agree with the various assumptions used to develop the estimates of costs of the interventions package reported in this document. However, the tool has been developed in such a way that it can be used by country investigators to estimate costs based on their specfic epidemiolgical, economic and political contexts as well as their policies and capacity of their national programmes in implementing the key prevention and control measures.

1. Introduction

1.1 Policy context and rationale

Concern is growing about the escalating global burden of noncommunicable diseases (NCDs) such as cardiovascular diseases, cancer, diabetes and chronic respiratory diseases. The concern is not just epidemiological but also economic. NCDs, which are often accompanied by long-standing disabilities, have a direct economic impact on households and communities, both through the uptake of health services and goods that diverts expenditure, but also on levels of income or labour productivity (Abegunde et al. 2007; WHO, 2005).

Despite the scale of these adverse consequences, NCDs have been neglected in international health and development initiatives. UN A/64/265 resolution 'Prevention and control of noncommunicable diseases' (UN, 2010) provides a high-level political mandate to develop an international policy framework for the prevention and control of NCDs. Key to this strategy is the generation of evidence on effective interventions that are affordable for developing regions.

There is growing evidence for and consensus about interventions that can tackle the leading NCDs and their underlying risk factors: tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol (WHO, 2011a). On a population level, these measures include reducing consumption of tobacco, alcohol and salt; improving awareness of healthy lifestyles; increasing excise and tobacco taxes and enhancing regulation. Interventions for individuals focus on prevention and treatment e.g. primary and secondary prevention of heart disease and stroke, as well as early detection, diagnosis, treatment and follow-up for cancers, diabetes, asthma and chronic obstructive pulmonary disease (WHO, 2010a).

Part of the evidence for increasing investment and implementation of priority interventions is economic. Cost-effectiveness information can help identify which interventions offer greatest value for money. Many economic studies have been conducted on NCD prevention and control, but a large proportion of these studies are from high-income countries, making comparisons and generalization problematic. However, a small sub-set of comparative analyses have been carried out for low- and middle-income countries, mainly through the Disease Control Priorities project (www.dcp2.org) and WHO's CHOICE programme (www. who.int/choice), which provide a sufficient, if imperfect, evidence base for setting priorities in these contexts (see Appendix 1c).

Along with evidence on the effectiveness and cost-effectiveness of policy and treatment options, information is needed on their feasibility, affordability and acceptability. Some work has been conducted on the costs of scaling up NCD interventions, such as population-based strategies to reduce tobacco use and dietary salt intake, plus combination drug therapy for people at elevated risk of a cardiovascular event within the next 10 years (estimated for 23 large, low- and middle-income countries for the period 2006-2015) (Asaria al. 2007; Lim et al. 2007). Cost-effective NCD interventions have been proposed at a WHO meeting for individuals in resource-constrained settings (WHO 2010a). More recently, the Global Status Report on Noncommunicable Diseases 2010 provided concrete recommendations on cost-effective interventions that are affordable in all countries - actions that should be undertaken immediately to accelerate results in terms of lives saved, diseases prevented, and costs avoided (WHO, 2011a). Feasibility and costing studies have also been conducted using a primary health care approach in resource-constrained settings (Mendis et al. 2010; Soliman et al. 2010; Ndindjock et al. 2011; Mendis et al. 2011).

What has been missing is a complete estimate of the costs of scaling up a core set of effective population-based and individual health-care interventions for NCDs and their major risk factors. This gap has represented a serious impediment to resource mobilization and financial planning at global and national levels. The current study has been carried out with a view to addressing it.

1.2 Scope, purpose and objectives

The aim was to develop a financial planning tool for scaling up delivery of a set of cost-effective population-based and individual-level health care interventions in low- and middle-income countries. This tool can be used to forecast financial resource needs at national or sub-national level and also to generate a price tag at global level. It will enhance traditional budgeting mechanisms in countries and provide information to development agencies and international institutions on the resources needed to address the growing burden of NCDs. The tool does not, however, assess the health impact or effects of interventions as a result of scaling-up, nor is it a cost-effectiveness evaluation tool.

Initial development of the tool was a collaboration between the Noncommunicable Disease and Mental Health (NMH) and Health Systems and Services (HSS) Clusters at WHO headquarters in Geneva. NMH holds the policy brief in this area and provided information for the intervention package and evidence-based protocols; HSS provided expertise in costing methods and tool development. Throughout this process, institutional partners were consulted to obtain country-level data and advice on the content and structure of the tool.

The impetus for this project is the UN High-Level Meeting on NCDs in September 2011. The deliverables are:

■ Construction of a resource needs/costing tool

■ Generation of a multi-country database containing values for all model parameters

■ Documentation of methods and results, including an estimate of the cost of implementation of the NCD intervention package, based on the 'best buys' interventions recommended in WHO's Global Status report 2010.

The tool requires a number of data sources. Assumptions have thus been made regarding the interventions being scaled up, pace of scale-up and level of coverage achieved. These may not coincide with a particular country's intentions or health system capacities. The tool has therefore been developed in such a way that it can be readily used by country investigators, and adapted to the specfic epidemiolgical, economic and political context.

2. Methods

2.1 Principles and practice of costing the scale-up of health services

The NCD costing tool is based on a methodology used to derive global price tags for scaling up interventions related to the Millennium Development Goals (MDGs), including HIV/AIDS, TB, malaria and child health (see for example Johns et al. 2007; Kiszewski et al. 2007; Stenberg et al. 2007).

These methods have also been applied to NCDs and mental health (Asaria et al. 2007; Lim et al. 2007; Chisholm et al. 2007), including an estimation of the costs and effects of scaling up strategies to reduce tobacco use and dietary salt intake, plus combination drug therapy for individuals at elevated risk of a cardiovascular disease (CVD) event.

Principles underlying the methodology are summarized in Box 1. The purpose is to identify the actual budgetary resources needed to implement efficient policies, as opposed to assessment of the economic value of resources used in an intervention, which might also include resources that have no financial value, such as voluntary care. In short, the methods and purpose of a costing tool are not the same as those of a cost-effectiveness tool.

Box 1. Costing principles

Financial versus economic costing: Costs reflect actual expenditures that need to be mobilized - from a broadly defined health-system perspective. Financial costs incurred but not usually paid for by the health system, notably travel costs of patients and families, are not included. Costs such as travel time and lost productivity, which have an economic if not a financial value, were likewise excluded.

Total versus incremental costing: The total cost for a given year is calculated for the entire population in need at the specified level of coverage, and is not adjusted for existing expenditures. For incremental costing, it is assumed that expenditure associated with current interventions continues to be made available. This means that only resources and expenditures required above current spending levels are included.

Separate costing of variable and fixed costs: Variable costs, including treatment, depend on the number of patients in need and the projected level of coverage. By contrast, capital costs (e.g. equipment and buildings) do not vary with each patient treated. In addition, programme costs incurred above the level of service delivery, such as district or national training and supervision, were estimated, including assessment of the capacity of each country's current health system to manage and monitor scale-up.

Use of country-specific data: Prices for 'non-traded' goods and need for services may vary greatly among countries, so country-specific data should be used to build costing estimates.

The cost of scaling up an intervention can be determined by using the following parameters:

■ population (of the country or region)

■ prevalence and incidence (of the disease or risk factor in question)

■ coverage (the proportion of population in need that is exposed to or receiving the intervention)

■ resource quantities (needed to implement the intervention; e.g. human resources, medicines, equipment)

■ prices or unit costs (for each resource item or entity; e.g. salaries, drug prices).

Box 2. Example of how to estimate the cost of scaling-up an intervention

A 20% rate of prevalence of smoking in an adult population of one million would yield a target population in need of 200 000 individuals. All these individuals could benefit from a brief intervention offered in primary care that, say, costs US$1 per treated case to deliver.

If coverage of the brief intervention was currently only 10%, the total annual cost for delivering the intervention would be US$20 000 (200 000 times US$1 times 10%); once scaled up to a higher desired level of coverage (such as 50%), the total cost will have increased five-fold to US$100 000. The difference between the current and target level of coverage gives the incremental cost of scaling-up the intervention (a total of US$80 000).

Total or incremental costs can be divided by the total number of people in the population to give a cost per capita (in this instance, the annual cost per capita would rise from US$ 0.02 to US$ 0.10, an increment of US$0.08).

Multiplication of the first two parameters (population times prevalence) defines the population at risk or in need, while multiplication of the final two parameters (resource use times price) provides the cost per case treated or person exposed to the intervention. The remaining parameter, coverage, provides the main mechanism by which scale-up takes place over time. Box 2 illustrates how these different parameters contribute to estimating the costs of scaling up.

Analytical steps require:

- definition of the intervention package

- estimation of the current intervention versus levels of need and coverage in the population

- calculation of the year-on-year resource costs required over a specified period to reach desired coverage.

The tool can produce estimates of total and incremental costs of scaled up provision, broken down by:

- category of intervention (e.g. population-wide interventions versus individual health-care interventions);

- cost category (e.g. human resources, physical capital)

- activity (e.g. regulation versus individual treatment)

- time (e.g. costs at five and 10 years).

The tool will allow country users to change default values, timelines or scale-up patterns. As mentioned earlier, the purpose of the tool is to aid financial planning for scaling up interventions that have been prioritized: it is not a cost-effectiveness or priority-setting tool.

2.2 Selection of diseases, risk factors and intervention strategies
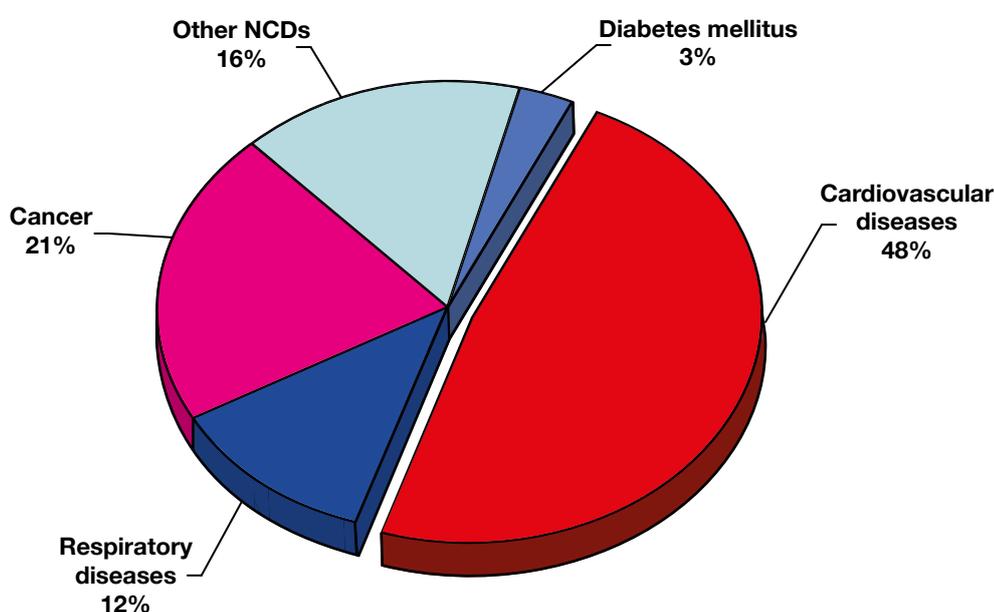
Selection of diseases (and risk factors)

A critical question to address in a costing exercise is its scope: which diseases, risk factors and interventions are to be included.

The reference point adopted for this study is the 2008-2013 Action Plan for the WHO Global Strategy for the Prevention and Control of Noncommunicable Diseases (WHO, 2008a), which focuses on four diseases: cardiovascular disease (CVD), cancer, diabetes and chronic respiratory disease. These diseases are responsible for the majority of deaths caused by NCDs (Figure 1) and are largely caused by four shared behavioural risk factors: tobacco use, harmful alcohol use, physical inactivity and unhealthy diet. Prevention of renal disease is included within the analytical framework through its link to CVD and

diabetes, as is the prevention of alcoholic liver disease via reduction in harmful use of alcohol.

By restricting analysis to these diseases and risk factors, other NCD conditions that account for a significant portion of the global burden of disease, such as other renal and liver diseases, gastrointestinal diseases, neurological diseases (other than stroke) and mental disorders, have been excluded. It will be important to bear this in mind when considering results. In the case of mental disorders, estimates of the cost of scaling up interventions have already been made for low- and middle-income resource settings (Chisholm et al. 2007).

Figure 1. Distribution of global NCD by cause of death, both sexes

Other NCDs
16%

Diabetes mellitus
3%

Cancer
21%

Cardiovascular
diseases
48%

Respiratory
diseases
12%

(Source: WHO, 2008b)

Selection of interventions for prioritized scale-up

Many interventions exist for prevention and control of NCDs. Even the wealthiest countries, however, have to make choices about which of these are implemented, because resources for health are finite - and in most countries, very limited. A number of criteria inform these decisions, including the current and projected burden of diseases (or their underlying risk factors, such as tobacco use), the cost-effectiveness, fairness and feasibility of implementing interventions and political considerations[1].

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1 Cost-effectiveness summarizes the efficiency with which an intervention produces health outcomes. A 'highly cost-effective' intervention is defined as one that generates an extra year of healthy life (equivalent to averting one disability-adjusted life year) for a cost that falls below the average annual income or gross domestic product (GDP) per person in the country or region in question.

In preparation for the 2011 UN High-level meeting on NCDs, WHO has identified a set of evidence-based 'best buy' interventions that meet these criteria (WHO, 2011a; WHO, 2011b). A best buy is a concept that extends beyond economic efficiency or cost-effectiveness. It is an intervention with compelling evidence for cost-effectiveness that is also feasible, low-cost and appropriate to implement within the constraints of the local health system. Interventions that do not meet all of these criteria - but which offer good value and have other attributes that recommend their use - can be characterized as 'good buys'. Policy-makers can consider best buys as a core set of interventions for priority scale-up, and good buys as an expanded set of interventions to be made available when resources allow.

Appendices 1a and 1b provide summary tables of interventions identified as best buys after the application of priority-setting criteria (avoidable burden, cost-effectiveness, implementation cost and feasibility). Appendix 1c provides data sources used for populating the cost-effectiveness dimension. Table 1 provides a summary list of two categories of interventions: population-based measures addressing NCD risk factors; and individual-based interventions addressing NCDs within the context of primary care.

Table 1. Summary of interventions included in the core scaling-up costing scenario

Core intervention set: Best buys	
Population-based interventions addressing NCD risk factors	■ Tobacco use: Tax increases; smoke-free indoor workplaces and public places; health information and warnings about tobacco; bans on advertising and promotion ■ Harmful alcohol use: Tax increases on alcoholic beverages; comprehensive restrictions and bans on alcohol marketing; restrictions on the availability of retailed alcohol ■ Unhealthy diet and physical inactivity: Salt reduction through mass media campaigns and reduced salt content in processed foods; replacement of trans-fats with polyunsaturated fats; public awareness programme about diet and physical activity
Individual-based Interventions addressing NCDs in primary care	■ Cancer: Prevention of liver cancer through hepatitis B immunization; prevention of cervical cancer through screening (visual inspection with acetic acid [VIA]) and treatment of pre-cancerous lesions ■ CVD and diabetes: Multi-drug therapy (including glycaemic control for diabetes mellitus) to individuals who have had a heart attack or stroke, and to persons with a high risk (> 30%) of a CVD event in the next 10 years; providing aspirin to people having an acute heart attack

This set of NCD best buy interventions forms the basis of the cost analysis presented here.

2.3 Assessment of epidemiological need and intervention coverage

Identification of the population in need

Comparable country-specific estimates of the prevalence of tobacco use, obesity and insufficient physical inactivity were drawn from the Global Status Report on Noncommunicable Diseases 2010 (WHO, 2011a). Estimates of the prevalence of harmful alcohol use were derived by triangulating aggregate adult per capita consumption with multi-country survey data on the distribution of alcohol use (by age and sex), using a statistical model developed by Rehm et al. (2010).

The prevalence of tobacco use, high blood pressure, raised cholesterol and raised blood glucose was also used to estimate - by age and sex - the proportion of the population at varying levels of total risk of experiencing a (fatal or non-fatal) CVD event during the next 10 years. WHO sub-regional values from the Comparative Risk Assessment study (WHO, 2009) were used to generate disaggregated estimates of risk exposure by age and sex, which are unavailable at country level. Rates of incidence or prevalence for CVD, diabetes, cancers and respiratory disorders were taken from WHO regional estimates produced by the Global Burden of Disease study (WHO, 2008b).

Scale-up period and country selection

The period of scaling up was set at 2011-2025, which is consistent with the set of targets indicators that are being drawn up for consideration by WHO Member States. The focus of analysis was on low- and middle-income countries but the tool can also be used in high-income countries.

Analysis was carried out for 42 low- and middle-income countries (each with more than 20 million people). These account for 90% of the NCD burden in developing regions of the world, and 77% of the global NCD burden. The 42 countries were grouped by income, as shown in Table 2. Estimates of total costs for all low- and middle-income countries were approximated by multiplying results for the 42 countries - which account for 90% of the population in developing regions - by a factor of 1.11 (100% / 90%).

Table 2. Low- and middle-income countries included in the analysis

Low-income countries (13)	Afghanistan; Bangladesh; Côte d'Ivoire; Democratic People's Republic of Korea; Democratic Republic of the Congo; Ethiopia; Kenya; Myanmar; Nepal; Nigeria; Sudan; Uganda; United Republic of Tanzania
Lower middle-income countries (13)	Egypt; Ghana; India; Indonesia; Iraq; Morocco; Pakistan; Philippines; Sri Lanka; Ukraine; Uzbekistan; Viet Nam; Yemen
Upper middle-income countries (16)	Algeria; Argentina; Brazil; Colombia; China; Islamic Republic of Iran; Kazakhstan; Malaysia; Mexico; Peru; Romania; Russian Federation; South Africa; Thailand; Turkey; Bolivarian Republic of Venezuela

Coverage levels and scale-up patterns

To calculate the additional resources required to reach the 2025 target, current coverage rates need to be established. For most strategies and countries included in the analysis, intervention-specific data on current effective coverage are not available. What is known, however, is that current effective intervention coverage is very low. Even for tobacco control, analysis has demonstrated that - with the exception of monitoring - the world's population covered by demand reduction measures of the WHO Framework Convention on Tobacco Control in 2008 was below 10% (WHO, 2011a).

The exception to this is hepatitis B immunization, for which country-specific data collated by WHO and UNICEF indicate high levels of (third-dose) coverage (WHO, 2010b). In 33 of the 42 countries in this study, coverage already exceeds 80%. Accordingly, expenditures for this intervention do not pose an additional resource requirement - except in the few countries where coverage continues to fall below this high coverage level.

For all other best buy individual interventions delivered in primary care settings, a default rate of 5% was adopted for current coverage. The target coverage level for these interventions was set at 80% for 2025. Individual countries may choose to adopt different target coverage levels when applying the model, depending on their policies, plans and resources.

The pace at which countries are able to scale up services also differs according to prevailing levels of infrastructure, human resource capacity and financial security as well as other competing priorities. Figure 2 illustrates three distinct patterns of scale-up, which were applied to countries as follows:

■ exponential scale-up (used for low-income countries): after an initial slow degree of health system development, coverage speeds up exponentially as the target year approaches

■ s-curve scale-up (used for lower middle-income countries): after a brief period of slow expansion, coverage escalates at a linear rate

■ front-growth scale-up (used for upper middle-income countries): this pattern assumes that much of the capacity to scale up is already in place, meaning that coverage can escalate rapidly within the short to medium term.

For population-based measures (such as changes in fiscal policy, new regulations or mass media campaigns), a different approach was required. For these interventions, four stages of policy implementation were used to identify resource needs over time:

■ planning stage (Year 1)

- policy development (Year 2)

- partial implementation (Years 3-5)

- full implementation (Year 6 onwards)

For countries with low levels of policy implementation, it was assumed that all stages of policy implementation would need to take place; for the very few countries already operating at a high level, only the resource costs of sustaining full implementation were included.

The current performance of countries with respect to tobacco control policy was assessed using data collated as part of the WHO report on the global tobacco epidemic (WHO, 2011c), which contains country-specific scores for each of the MPOWER package components (see Appendix 2a). Similarly for alcohol control policy, data were extracted from a recent global survey on alcohol and health (see Appendix 2b). For diet and physical activity, country-specific performance data were not available; given the very low levels of policy implementation for these two NCD risk factors, all countries were assumed to require all four stages of policy implementation.

Figure 2. Patterns of intervention scale-up
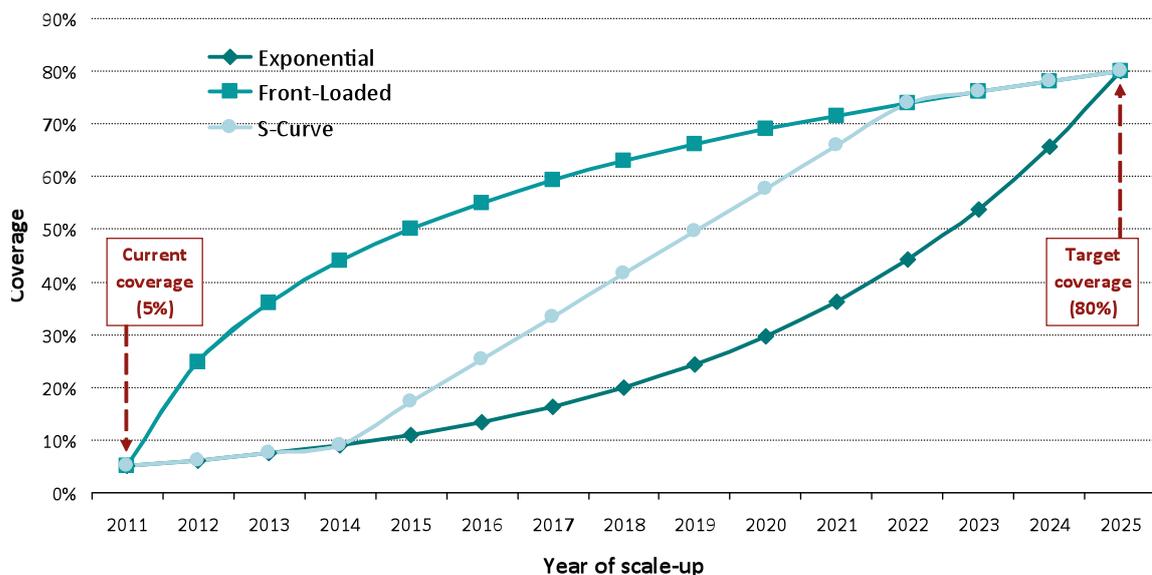
2.4 Estimation of resource needs and unit costs

For individual interventions delivered in primary-care settings, the resource components consist of human resources, medicines, laboratory services and diagnostic and therapeutic procedures. Estimation of the quantity of these resources needed is based on treatment guidelines and clinical protocols, in particular the WHO guidelines for assessment and management of cardiovascular risk and the PEN package guidance (WHO, 2007; WHO, 2010a; see Appendix 3 for the PEN protocol for the integrated management of hypertension and

diabetes, and Box 3 for the resource profile related to multi-drug therapy for individuals at >30% CVD risk).

Box 3. Resource use profile for multi-drug therapy (individuals at >30% CVD risk)

Screening stage:

- Primary care visits: one five-minute visit (all cases)
- Laboratory tests: urine sugar analysis (all cases); blood glucose, cholesterol, urinanalysis (30% of cases)

Treatment stage:

- Primary care (counselling, risk assessment): four annual visits, five minutes each (all cases); four annual visits, 20 minutes each (all cases with diabetes)
- Medicines (daily dose, % cases): hydrochlorothiazide (25 mg, 95%), enalapril (20 mg, 60%), atenolol

(75 mg, 50%), amlodipine (5 mg, 60%), simvastatin (15 mg, 100%) and where applicable, metformin (2000 mg, 100% of cases with diabetes; for the majority of cases, the actual dose required may vary between 1000-2000 mg per day).

For population-based measures, a resource needs matrix was developed, consisting of the four stages of policy development described earlier and six categories of resource use: human resources; training; meetings; mass media; supplies and equipment; and other resources. Box 4 illustrates activities that were considered necessary at different stages of policy development when identifying resource needs for certain tobacco control measures. Table 3 provides more generic examples of activity-based resources that were quantified.

Box 4. Tobacco control actions, by stage of policy development

Smoke-free policies

- Year 1 – Evidence base is prepared; public consultation launched
- Year 2 – Legislation and regulations drafted; enforcement plan and training programme designed; media strategy developed
- Year 3 – Public and employer information campaign launched; legislation passed; inspections and test-case prosecutions initiated
- Ongoing – Regular inspections, enforcement and media advocacy maintained

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Pack warnings

- Year 1 – Evidence base is prepared; public consultation launched
- Year 2 – Legislation and regulations drafted; enforcement plan and training programme designed; media strategy developed
- Year 3 -– Public and retailer information campaign launched; legislation passed; inspections and test-case prosecutions initiated
- Ongoing – Regular inspections, enforcement and media advocacy maintained
- Warnings rotated every two years

Advertising ban

- Year 1 – Evidence base is prepared; public consultation launched
- Year 2 - Legislation and regulations drafted; enforcement plan and training programme designed; media strategy developed
- Year 3 – Public and retailer information campaign launched; legislation passed; inspections and test-case prosecutions initiated
- Ongoing – Regular industry monitoring and media advocacy maintained

Table 3. Resource needs matrix for population-based NCD prevention measures

Stage of policy development	Human resources	Training	Meetings	Mass media	Supplies and equipment	Other
Planning (Year 1)	Programme management; administration	Strategy / policy analysis	Stakeholders		Office equipment	Baseline survey
Development (Year 2)	Advocacy; law	Legislation	Intersectoral collaboration	Awareness campaigns		Opinion poll
Partial implementation (Years 3-5)	Inspection	Regulation	Monitoring	Counter-advertising	Vehicles, fuel	
Full implementation (Year 6 onwards)	Enforcement		Evaluation			Follow-up survey

A further dimension of the resource needs matrix relates to the level of administration (central, provincial or district). To derive comparable estimates of resource needs across interventions, a standardized country of 50 million people was assumed (split into 10 provinces of

5 million and 10 districts of 0.5 million persons). An example of the human resource needs estimated for this population is provided in Appendix 4a (for smoke-free policies). These standardized estimates were adjusted to reflect the actual population size and administrative composition of each country (see Appendix 4b for an example of how human resource needs for smoke-free policies were calculated for an actual country with a population of 160 million split into seven provinces and 64 districts).

The same process was used for the other resource categories. The cost of training and meetings was based on the frequency of meetings and workshops within a year, their average duration, the number of national and sub-national participants (plus associated support staff), and the size of the meeting venue. For mass media, TV and radio advertising, newspaper advertisements, wall posters and information leaflets were included. Estimates were based on the number and intensity of media slots, for example four, two-week series per year, each consisting of 10 one-minute TV and radio slots per week.

Unit costs for resource items were taken from the WHO-CHOICE database (www.who.int/choice/costs), which contains country-specific estimates for primary care visits of different durations, salaries, per diem allowances (for training and meetings), media costs and consumable items, including fuel and office supplies. Generation of these estimates was based on an econometric analysis of a multinational dataset, using gross national income per capita (plus other explanatory variables) to predict unit costs in different WHO Member States (for more information, see Adam et al. 2003; Johns et al. 2003, 2008). Drug prices were taken from the International Drug Price Indicator guide, with adjustments made for the cost of carriage, insurance and freight, as well as country distribution (multipliers taken from the WHO-CHOICE database). All prices are expressed in US dollars for 2008 (no account is taken of inflation).

Resource-use profiles and unit cost values can be amended by countries interested in applying the costing tool to their own contexts.

3. Results

3.1 Cost of scaling up 'best buy' interventions for NCD risk factors
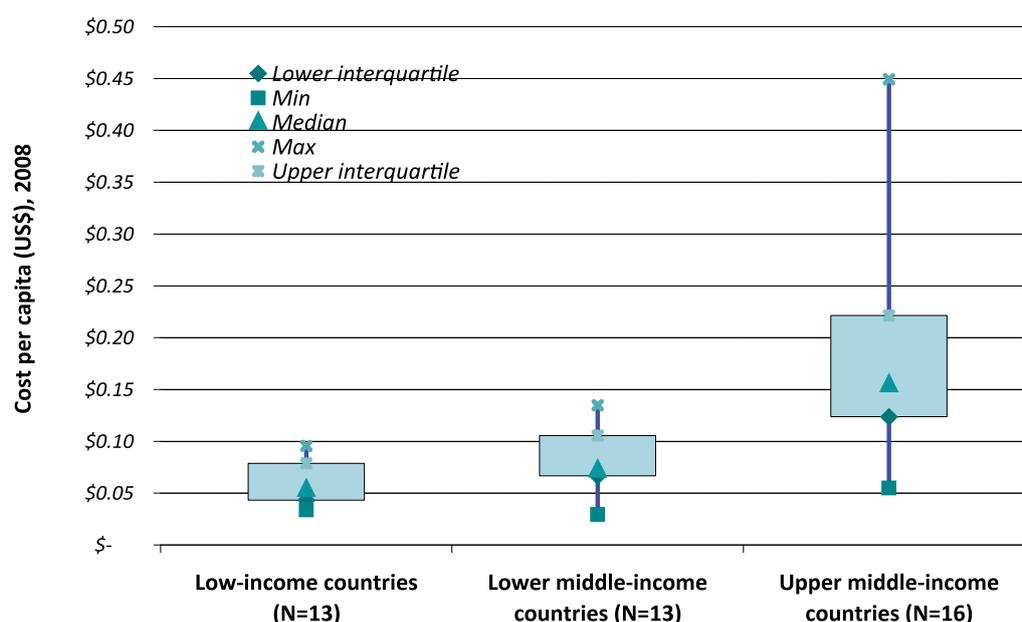
Tobacco control

The total annual cost of four population-based demand reduction best buy measures of the Framework Convention on Tobacco Control – including overall programme management and media support – is projected to be US$0.6 billion for all low- and middle-income countries, or US$0.11 per capita (Table 4). The largest cost is related to media campaigns.

Table 4. Estimates for the average annual cost of tobacco control best buy interventions in all low- and middle-income countries (US$ 2008)

Intervention	Total annual cost (US$)	Annual cost per person (US$)	Share of cost (%)
Program Strategy Development	$ 64,252,725	$ 0.011	10%
Smoke-free policies	$ 87,953,502	$ 0.016	14%
Raise tobacco taxes	$ 28,506,069	$ 0.005	5%
Package warnings	$ 40,705,857	$ 0.007	7%
Advertising bans	$ 45,062,561	$ 0.008	7%
Media campaigns	$ 353,639,300	$ 0.062	57%
Total	$ 620,120,015	$ 0.110	100%
Resource category	Total annual cost (US$)	Annual cost per person (US$)	Share of cost (%)
Human resources	$ 232,474,950	$ 0.041	37%
Training	$ 20,056,233	$ 0.004	3%
Meetings	$ 8,277,164	$ 0.001	1%
Mass media	$ 337,984,848	$ 0.060	55%
Supplies and Equipment	$ 16,694,112	$ 0.003	3%
Other programme costs	$ 4,692,708	$ 0.001	1%
Total	$ 620,120,015	$ 0.110	100%

As shown in Figure 3, implementation costs vary by income level; the median cost per capita ranges from as little as US$0.05 in low-income countries to US$0.15 in upper-middle income countries. After initial planning in Year 1, the annual cost does not vary appreciably over the remaining scale-up period; that is, a constant investment is needed, first to develop or reframe policies, and in later years to maintain a comprehensive level of enforcement.

Figure 3. Median cost per capita of scaling up tobacco control best buy interventions in low- and middle-income countries (US$ 2008)


Alcohol control

Results for alcohol control are similar to those for tobacco control, with total costs per year amounting to US$0.78 billion (Table 5).

Table 5. Estimates for average annual cost of alcohol control best buy interventions in all low- and middle-income countries (US$ 2008)

Intervention	Total annual cost (US$)	Annual cost per person (US$)	Share of cost (%)
Restrict access to retailed alcohol	$ 344,980,900	$ 0.061	44%
Enforce bans on alcohol advertising	$ 36,386,931	$ 0.006	5%
Raise taxes on alcohol	$ 24,546,845	$ 0.004	3%
Monitoring	$ 54,538,088	$ 0.010	7%
Advocacy support / partnerships	$ 318,360,099	$ 0.056	41%
Total	$ 778,812,863	$ 0.138	100%
Resource category	Total annual cost (US$)	Annual cost per person (US$)	Share of cost (%)
Human resources	$ 287,908,847	$ 0.051	37%
Training	$ 17,661,797	$ 0.003	2%
Meetings	$ 5,525,637	$ 0.001	1%
Mass media	$ 448,131,507	$ 0.079	58%
Supplies and equipment	$ 18,217,176	$ 0.003	2%
Other programme costs	$ 1,367,899	$ 0.000	0%
Total	$ 778,812,863	$ 0.138	100%

These costs are driven by human resource needs for programme management and enforcement of alcohol-related laws and policies as well as media-related expenses. The greater variability around the typical (median) cost of implementation (see Figure 4) results from large underlying differences in the prevalence of alcohol use at population level; these interventions were not accounted for in countries with an adult prevalence of harmful alcohol use below 1%.

Figure 4. Median cost per capita of scaling up alcohol control best buy interventions in low- and middle-income countries (US$ 2008)
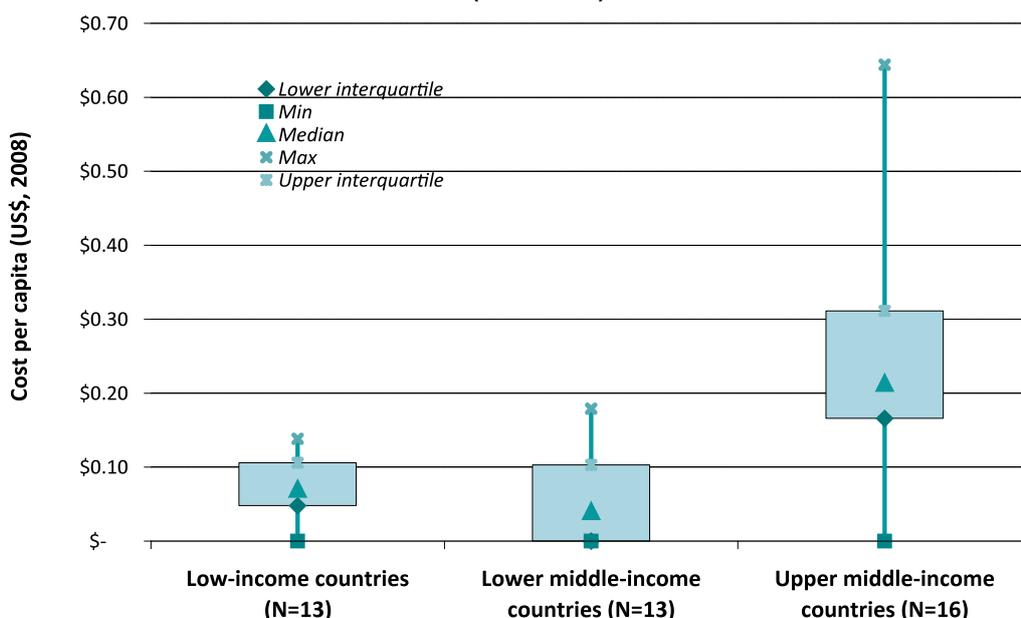
Improving diet and physical activity

The cost of implementing three best buy interventions for unhealthy diet and physical inactivity is low (less than US$0.10 per person, or $435 million per year for all low- and middle-income countries; see Table 6). Again, the largest public health expenditure involved in implementing these strategies is mass media associated with general and salt-specific health promotion and awareness campaigns.

Table 6.Estimates for average annual cost of best buy interventions for addressing unhealthy diet and physical inactivity (US$ 2008)

Intervention	Total annual cost (US$)	Annual cost per person (US$)	Share of cost (%)
Promote public awareness about diet and physical activity	$ 213,042,290	$ 0.038	49%
Reduce salt intake	$ 169,581,224	$ 0.030	39%
Replace trans fat with polyunsaturated fat	$ 52,685,944	$ 0.009	12%
Total	$ 435,309,458	$ 0.077	100%

Resource category	Total annual cost (US$)	Annual cost per person (US$)	Share of cost (%)
Human resources	$ 79,324,835	$ 0.014	18%
Training	$ 12,255,133	$ 0.002	3%
Meetings	$ 4,216,617	$ 0.001	1%
Mass media	$ 333,636,765	$ 0.059	77%
Supplies and equipment	$ 5,876,108	$ 0.001	1%
Other programme costs	$ -	$ -	0%
Total	$ 435,309,458	$ 0.077	100%

A similar income gradient for other NCD risk factors is apparent from Figure 5, which shows that upper-middle income countries can expect to spend at least twice as much as low-income countries, due to the higher costs such as salaries and media expenses.

Figure 5. Median cost per capita of scaling up diet and physical activity best buy interventions in low- and middle-income countries (US$ 2008)
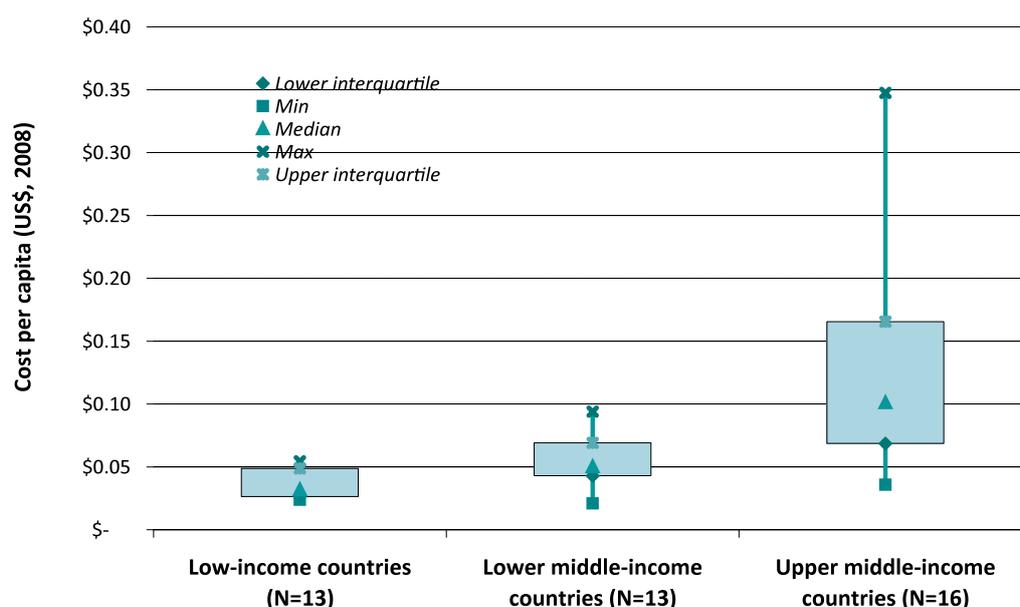

Combined estimates for cost of scaling up best buy interventions for NCD risk factors

The total cost of resource requirements for all best buy intervention strategies for addressing tobacco and harmful alcohol use, as well as unhealthy diet and physical inactivity approaches US$2 billion per annum for low- and middle-income countries (Figure 6). After the planning phase in Year 1, costs do not vary substantially from year to year. The small elevations in years 2016 and 2021 reflect the cyclical

replacement of office and other equipment, which are assumed to last five years. The higher cost in Year 2 (policy development stage) is due to initial training, legislation and health promotion efforts.

Figure 6. Total estimated cost of scaling up best buy interventions for NCD risk factors in all low- and middle-income countries (US$ billion 2008)
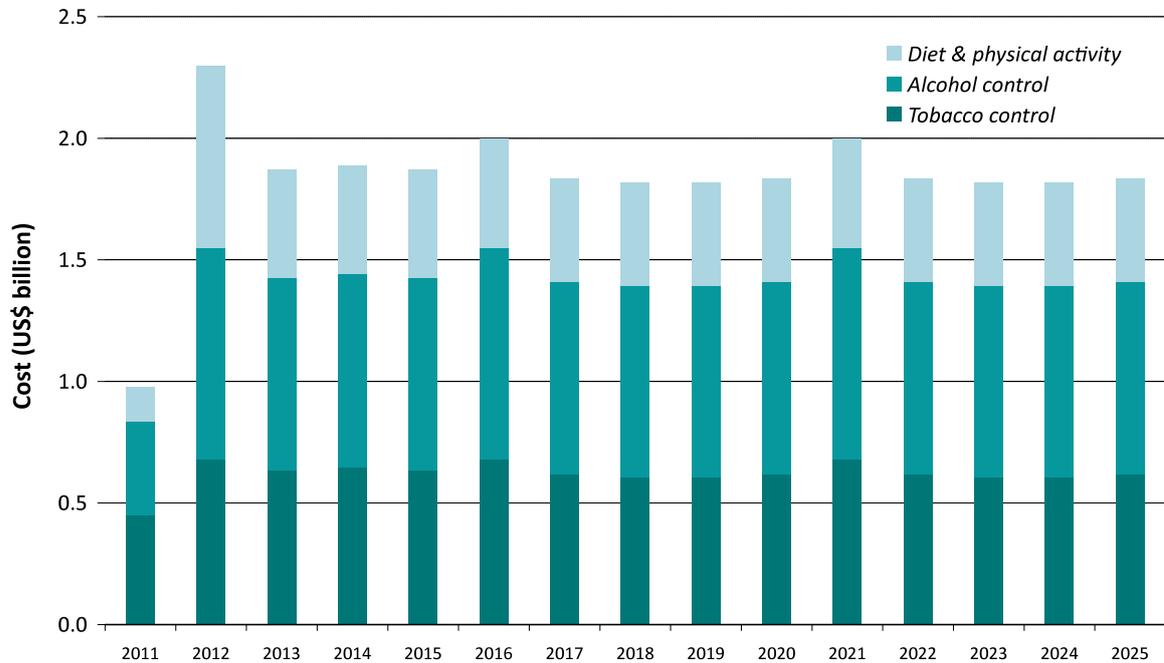
As shown in Figure 7, the median cost per capita in low- and lower-middle income countries amounts to less than US$0.20. For upper-middle income countries, the median cost is closer to US$0.50, exceeing US$1 per capita in a few cases.

Figure 7. Median cost per capita of scaling up best buy interventions for NCD risk factors in low- and middle-income countries (US$ 2008)
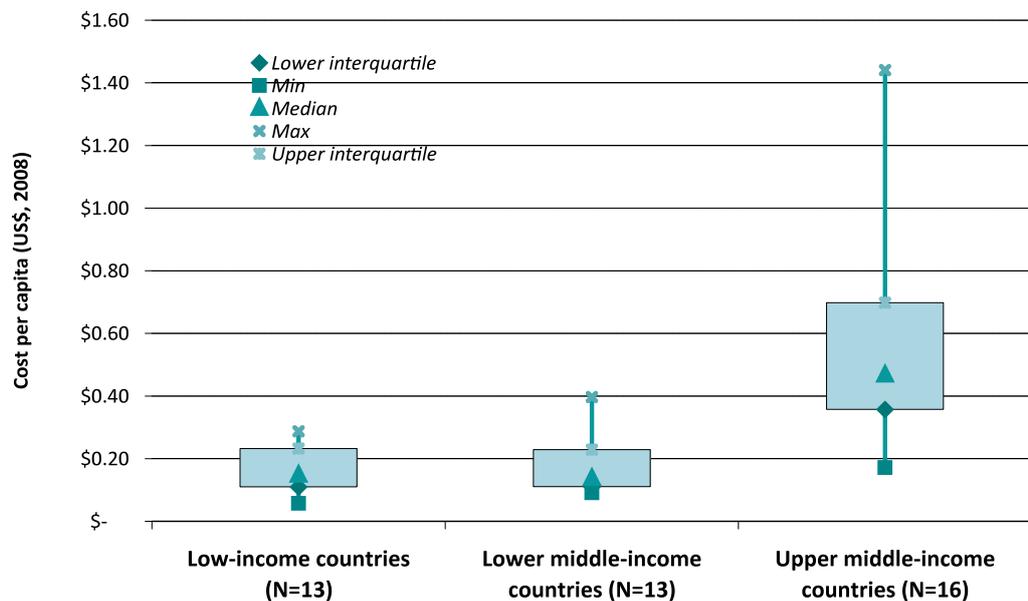
3.2 Cost of scaling up best buy interventions for NCDs

As discussed earlier, the best buys in primary care identified for individual-based care of NCDs include: multi-drug therapy for people with more than 30% CVD risk, including those with diabetes, established ischaemic heart or cerebrovascular disease; aspirin for people with an acute heart attack; prevention of cervical cancer by screening and referral for treatment of precancerous lesions; and hepatitis B immunization for the prevention of liver cancer. As mentioned before, hepatitis B immunization has already been scaled up in the large majority of countries, and does not therefore require additional resources to be made available, over and above what is already being committed.

Estimated costs cover primary care outpatient visits for consultation, counselling and procedures, auxiliary care, medicines and diagnostic and therapeutic procedures. The drivers of these estimates are population growth projections and the projected increase in treatment coverage.

The cumulative cost of scaling up these individual-level best buy interventions for all low- and middle-income countries is projected to be US$1 435 billion from 2011-2025. This amounts to an average of US$9.4 billion per annum, ranging from US$2 billion in 2011 to US$ 11.5 billion by 2025 (Figure 8).

Figure 8. Total estimated cost of scaling up individual-based best buy interventions for NCDs in all low- and middle-income countries (US$ billion 2008)
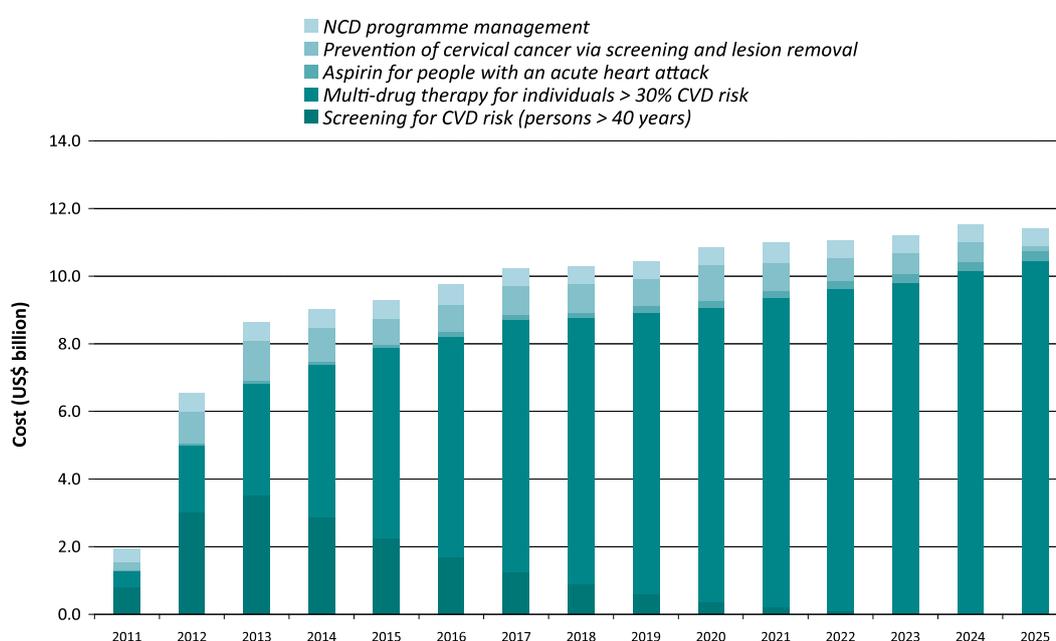

Figure 9 shows the same total cost summary, but displayed by resource category. Human and other resources involved in primary

care represents the largest category of cost in the early stages of scale-up, although medicines take an increasing share of total expenditure as treatment of individuals at high CVD risk is scaledup to target coverage levels.

Figure 9. Estimates on cost of scaling up individual-based best buy interventions for NCDs in low- and middle-income countries (US$ billion 2008), by resource category
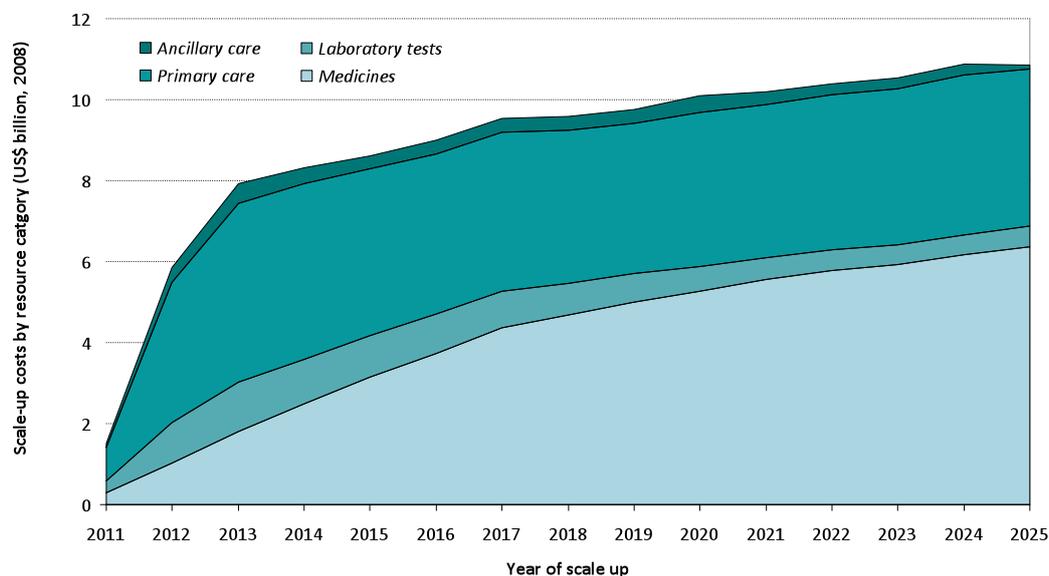
As with population-based preventive measures, the estimated cost of scalingup differs according to country income. Figure 10 shows that in low-income countries, the annual per capita cost of implementing individual-based NCD best buys averages less than US$1; in lower-middle income countries, it averages less than US$1.50 and in upper-middle income countries it averages US$2.50.

Figure 10. Mean estimated cost per capita of scaling up best buy interventions for NCDs in low- and middle-income countries (US$ 2008)

Cardiovascular disease and diabetes

The estimated cost of scaling up cardiovascular disease (CVD) and diabetes best buys in all low- and middle-income countries is over US$120 billion, with the annual average being a little over US$8 billion. This includes the cost of screening in primary care to detect individuals at risk of CVD, at a cost of US$3-5 per person screened. The cost of providing aspirin for people with acute heart attack at the primary care level (including visits, diagnostic tests and drugs, but excluding post-referral costs) ranges from US$13-15 per treated case (Table 7). By comparison, the annual cost per case of multi-drug therapy to those at high risk of a CVD event ranges from US$70 in low-income countries to US$105 in upper-middle countries.

As shown in Figure 8, providing aspirin to individuals with acute heart attack represents by far the smallest component of cost throughout the scale-up period. The multi-drug therapy intervention becomes the largest element as treatment coverage rates increase from their currently low base to a target level of 80%.

Cancer

The estimated cost of scaling up the prevention of cervical cancer is US$11.3 billion for the period 2011-2015. Estimates include the cost of one-off screening among women aged between 35-45 years using visual inspection with acetic acid (VIA), and treatment of precancerous lesions using cryotherapy for screen-positive cases. The cost per case is shown in Table 7. Other screening tests and strategies are also available, such as screening women aged 25-49 every three years using VIA or a pap smear test. Such strategies would be expected to have higher costs but may be a preferred option, particularly in countries at higher income levels.

**Table 7. Estimates for cost per treated case for individual-based NCD best buy interventions**

	Low-income countries	Lower middle-income countries	Upper middle-income countries
Screening in primary care for CVD risk (persons > 40 years)	$ 3.0	$ 3.9	$ 5.3
Multi-drug therapy for individuals (> 30% CVD risk)	$ 70	$ 84	$ 105
Multi-drug therapy for individuals (with heart disease)	$ 69	$ 85	$ 108
Multi-drug therapy for individuals (with stroke)	$ 66	$ 121	$ 206
Aspirin for people with an acute heart attack	$ 13	$ 13	$ 15
Prevention of cervical cancer through screening and lesion removal	$ 26	$ 46	$ 56

3.3 Total estimated cost of a best buy package for NCD prevention and control

The combination of population-based and individual-based best buy interventions for NCDs and their underlying risk factors gives rise to a cumulative cost of US$170 billion over the period 2011-2025, at an average of US$ 11.4 billion per year (Figure 11). This amounts to an annual per capita investment of under US$1 in low-income countries, US$1.50 in lower middle-income and US$3 in upper middle-income countries.

A large share of these costs relates to the individual-based provision of multi-drug therapy for those with a high CVD risk. Population-based measures aimed at reducing exposure to risk factors for NCDs - tobacco and alcohol use, unhealthy diet and physical inactivity - account for a small fraction of the total price tag (approximately US$2 billion per annum). Likewise, the cost of NCD programme management, which includes central, provincial and district level staff as well as training courses and media expenses, contributes very little to total cost estimates (US$0.5 billion per year).

Figure 11. Total estimated cost of scaling up NCD best buy interventions in all low- and middle-income countries (US$ 2008)
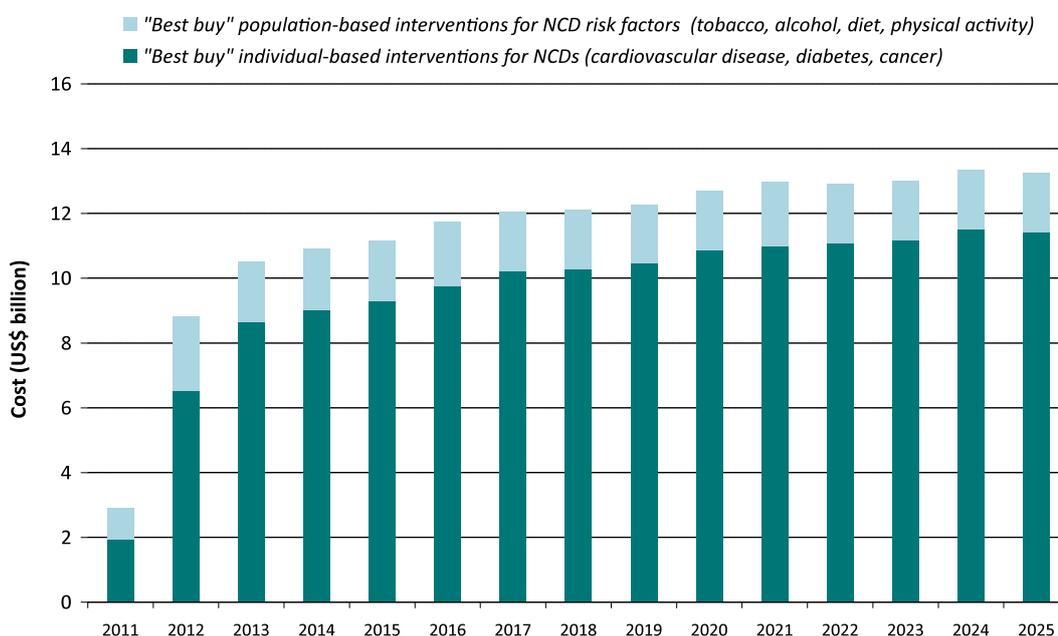
The budgetary implications associated with the implementation of this combined package in different income regions are summarized in Table 8. As a percentage of health-care spending in 2008, the average annual cost of the package represents 4% in low-income countries, 2% in lower middle-income countries and less than 1% in upper

middle-income countries. The proportion changes with the year of scale-up; this is shown in Figure 12.

Table 8. Estimated cost of best buy NCD intervention package as a percentage of total health expenditure

	Low-income countries	Lower middle-income countries	Upper middle-income countries
Total health expenditure per head	$ 22	$ 74	$ 412
Best buy NCD package per head (2011-2025 average)	$ 0.88	$ 1.45	$ 2.91
Best buy NCD package as percentage of total health expenditure	4.0%	2.0%	0.7%

For low-income countries, WHO (2010c) estimated for the High-Level Taskforce on Innovative International Financing for Health Systems that the total cost of a set of health services capable of meeting the MDGs amounts to US$44 per capita in 2009, rising to US$60 by 2015. These estimates include disease-specific costs for MDG-related conditions and also components of NCD-specific expenditure (medicines), as well as shared health system resources such as human resources and logistics. As a proportion of 2009 total cost estimates, the NCD best buy package described here amounts to approximately 2% (US$0.88 divided by US$44).

Figure 12. Total estimated cost of scaling up NCD best buy interventions as a proportion of total health expenditures in low- and middle-income countries
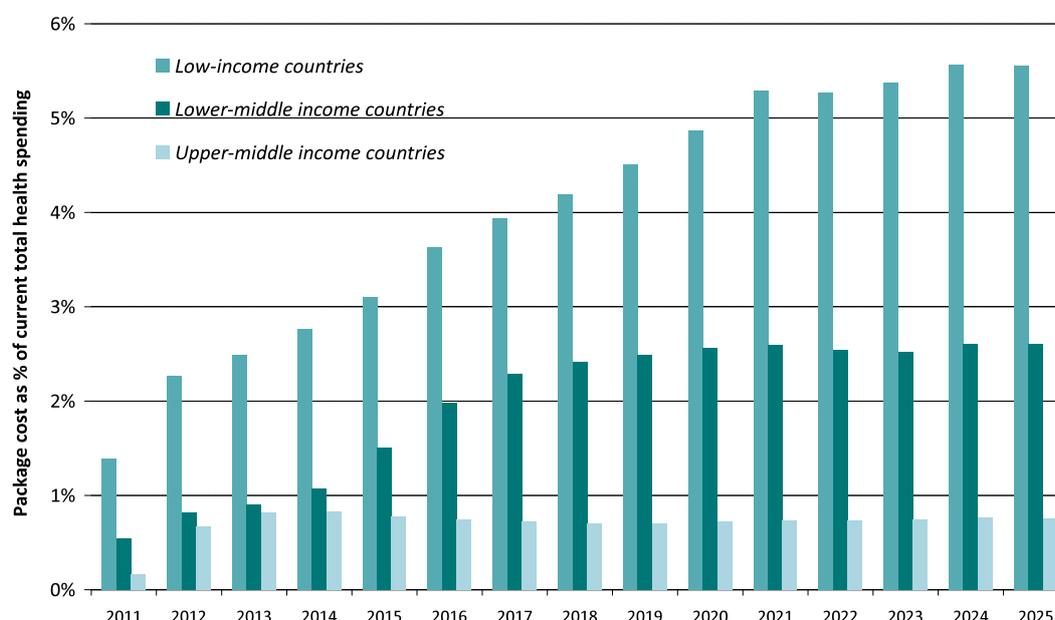
4. Conclusion

4.1 Main findings

This study is an initiative to estimate the resources needed to scale up a set of evidence-based intervention measures for NCD prevention and control. The analysis took as its reference point the 2008-2013 Action Plan for the WHO Global Strategy for the Prevention and Control of Noncommunicable Diseases (WHO, 2008a) and focused on estimating the cost of scaling-up prioritized intervention strategies in low- and middle-income countries over a period of 15 years (2011-2025), by which time all interventions are expected to have reached their target level of coverage.

The main finding of the study is that scaling up a set of best buy intervention across all low- and middle-income countries is estimated to cost approximately US$11.4 billion per year. This amount is equivalent to an annual investment of less than US$1 per person living in low-income countries, US$1.50 per person living in lower middle-income countries, and US$3 per person living in upper middle-income countries. Expressed as a proportion of current health care spending, the average annual cost of implementing such a package amounts to 4% in low-income countries, 2% in lower middle-income countries and less than 1% in upper middle-income countries.

4.2 Implications for health policy and resource allocation

There are several ways to interpret these costs:

■ From a public health perspective, an annual per capita investment of US$1-3 would appear to be a low price to pay for significantly reducing the enormous burden of disease from major NCDs and their underlying risk factors in lower-income countries.

■ From an economic perspective, the sums involved in mounting a scaled up NCD response are very small compared with the massive losses in gross national product or social welfare that would occur if no scaled up action and investment are taken - a scenario that takes into account anticipated trends in exposure to NCD risk factors as well as shifts in the size and structure of populations. An ongoing analysis undertaken for the UN High-Level Meeting on NCDs by the World Economic Forum and the Harvard School of Public Health has estimated that current losses in the national product of low- and middle-income countries over the same period

of 2011-2025 will run into trillions of dollars. Confronted with a loss of this magnitude, an annual outlay of US$10-12 billion appears to be a sensible investment.

■ However, the finances required to scale up the NCD response represent a new demand on health budgets, especially in relation to the very low levels of current expenditure on prevention and control of these diseases. While the potential budgetary impact on resources in upper middle-income countries is arguably low - less than a 1% increase for the best buy package - the impact in low-income countries is anticipated to be greater (where the package would require a 4% increase in total health spending). It should be noted that governments generate substantial revenues from taxes on tobacco products and alcoholic beverages, which could serve as an appropriate source of programme funding for NCD prevention and control.

■ Scale-up costs presented here can be compared with estimates for scaling up responses to other leading contributors to disease burden in low and lower-middle income countries , including HIV, TB, malaria and child health (Johns et al. 2007; Kiszewski et al. 2007; Stenberg et al. 2007). For the period 2006-2015, for example, estimated global resources needed per year amount to US$3.9-5.6 billion (US$0.73-1.03 per capita) for attaining universal coverage of maternal and newborn health services, and US$52.4 billion (US$0.47-1.46 per capita) for scaling up priority interventions in 75 countries for children under five years. When comparing these figures, however, it should be noted that baseline levels of MDG-related disease programme implementation are considerably higher. This means that the incremental cost of achieving coverage goals is diminished. By contrast, current levels of programme implementation or coverage for NCD control and prevention are comparatively low, meaning that the additional investment needed to reach a high level of coverage will be much more substantial. In addition, NCDs is an umbrella term that covers many preventable and treatable conditions (as opposed to a single disease).

The overall implication of these perspectives is that while much can be done to address the needs of populations at risk of NCDs, there are significant financial challenges for lower-income countries. By identifying the costs associated with a set of best buy interventions, this analysis provides options for action that can be considered even in very low-resource settings, including a number of population-based preventive measures that are cheap to initiate and sustain (less than US$0.20 per capita in low- and lower-middle income countries). Implementation of even this restricted set of measures, including tobacco control and salt reduction, will help to significantly reduce the escalating macroeconomic consequences of NCDs in these countries.

4.3 Study limitations and uncertainties

Financial modelling of the kind presented here inevitably requires a number of assumptions. Some of the main limitations are:

■ As outlined in Section 2.1, estimating the cost of scaling up health interventions involves a method that has been repeatedly used and draws on core information domains. Many data variables, including population and prevalence estimates as well as target coverage, are well established. Other data domains, in particular current coverage, programme resource requirements and country-specific processes for drugs or locally produced goods and services, carry a greater degree of uncertainty, either because of lack of up-to-date information (e.g. coverage rates, by country and intervention) or potential measurement error (e.g. predicted salary levels or the cost per primary care visit).

■ With respect to current coverage, the simplifying assumption was that coverage for individual-level interventions falls below 10% (a default level of 5% was used). Should current coverage levels be appreciably higher than this, the incremental costs of scaling-up would be that much less (meaning that the reported results are conservative).

■ Regarding resources at programme level, including programme management staffing levels, stakeholder meetings, training sessions and media - a standardized template and approach were used to avoid inconsistent costing across programmes; where available, estimates were compared with earlier cost-effectiveness or scaling-up studies that quantify these programme-level resources; many consultations were held with programme experts to generate realistic estimates of actual need at country level. Nevertheless, this is an area where there is little reported empirical evidence, meaning that values are largely based on expert opinion. Accordingly, this will represent a key area for country-level validation and contextualization.

■ For unit costs of non-traded goods and services (including salaries and unit costs of primary care visits), we relied on the WHO-CHOICE costing database, which has country-specific predictions that have been updated to 2008 price levels. Again, actual prices in 2008 for a specific country may have differed (up or down) by a small margin; it is not expected that the net effect of this price uncertainty would change baseline results substantially;

■ International medicine prices were adjusted for country-specific multipliers for transportation from border of entry to outlets. Data were not available for estimating the extent of mark-ups for medicines used in each country.

Costs of overcoming system-wide constraints, such as an inability to train and retain health professionals, are not addressed. A unified costing tool (OneHealth) is being developed by a multi-agency working group that will accommodate these issues; an NCD module is to be incorporated into this health system planning tool (http://www.internationalhealthpartnership.net/en/working_groups/working_group_on_costing).

The scope of the analysis was restricted to consideration of a set of core best buys for NCD control and prevention that has been identified through an evidence-based process. However, countries may choose to add to or subtract from this list in accordance with local priorities; therefore, a wider set of intervention strategies has been incorporated into the tool for country use (e.g. tobacco cessation, brief advice for heavy drinkers, early detection of breast cancer). In addition, the economic and other evidence underpinning the selection of the best buys is largely based on international and regional analyses and may not fit the circumstances of a particular country; for example, increased taxes on alcoholic beverages are not a highly cost-effective strategy in countries where consumption levels are low but the unrecorded (untaxed) proportion of this consumption is high (Anderson et al. 2009).

A further limitation of the modelling is that cost estimates do not take into account the impact of preventive measures on subsequent disease rates, such as the impact of tobacco control measures on future rates of ischaemic heart disease or stroke; rather, disease rates have been assumed to be constant throughout the scale-up period. As a consequence, total costs of scale-up presented here might be expected to be overestimated; however, it is also the case that in countries with positive population growth, more people will be exposed to NCD risk factors (such as tobacco or harmful alcohol use), thus mitigating the extent of overestimation. Even in countries with zero population growth, increased life expectancy will increase the population at risk.

Incorporation of these interactions requires the development and application of a sophisticated epidemiological model that includes all the major NCDs and their shared underlying risk factors. Such models, which typically require a microsimulation approach that will handle the many possible interactions that can occur with populations at risk, have been used in cost-effectiveness analyses (including for some of the interventions included in this study; Cecchini et al. 2010); they have also been used to assess the health effects of multi-drug therapy scale-up (Lim et al. 2007). However, it has not been possible within the time and funding constraints of this 2011 study to incorporate such modelling into the multi-intervention, year-on-year scaling-up scenarios used here.

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As a result, the analysis does not provide estimates of the health impacts associated with the combined implementation of the best buy strategies, in particular the number of premature deaths avoided as interventions are scaled-up. This information gap represents a key piece of analysis that would need to be undertaken to demonstrate the return on the large-scale investments indicated. Fortunately, earlier scaling-up analysis performed for tobacco control, salt reduction and multi-drug therapy - covering six of the 14 best buy interventions included here - has already demonstrated the enormous public health gain to be realized, namely, 32 million deaths over a 10-year period in 23 large developing countries (Asaria et al. 2007; Lim et al. 2007).

Finally, while this study describes the cost of responding to the burden of NCDs, it does not determine who will pay. That is a question for countries to consider, depending on their income and resource availability, as well as their institutional and infrastructural capacity to scale-up interventions and services. As discussed in the 2010 World Health Report (WHO, 2010d), there are three general mechanisms by which governments can generate resources for health (including renewed action on NCDs):

1. By increasing or ensuring a fair share of government spending on health (in general, or on NCD control and prevention in particular), which is a political process that can be advanced through coordinated action from health ministries and civil society;

2. By identifying new or diversified sources of revenues for health, for example, a national health insurance levy on value-added tax or increased excise taxes on alcoholic beverages or tobacco products;

3. If applicable, by exhorting external donors to meet their international commitments for official development assistance and to provide more predictable, long-term aid.

4.4 Next steps: country-level application and validation

The primary use of the tool is ultimately directed at the national level. The tool has been developed to be used with widely accessible software (Microsoft Excel) and by country investigators responsible for NCD programme planning or development. It is envisaged that a process of country-level adaptation in selected WHO Member States will commence shortly after the UN High-level meeting on the prevention and control of NCDs in September 2011. This process will be beneficial to country users and to the developers, through evaluation of the tool.

To optimize the flexibility and usefulness of the tool at national level, the set of interventions from which policy-makers and planners

can choose may need to go beyond the sub-set of best buys assessed here. Accordingly, resource-need profiles and cost estimates for other interventions have been integrated into the tool, to give countries a better sense of the resource implications associated with the delivery of a more comprehensive public health response to NCDs. However, given that implementation coverage of best buy strategies is still very modest in most low- and middle-income countries, it is expected that countries may first wish to focus on these best buy strategies before considering the broader financing and health system ramifications of an expanded package of care that can be delivered within primary care settings.

A further step relates to the transfer of the tool's content into One-Health, which will take the costing analysis to the next level, since it will enable NCD scale-up to be considered within the constraints of broader health system planning at national level. As part of the development of this NCD module within OneHealth, special attention will need to be given to modelling of composite as well as disaggregated health gains brought about by intervention; such an analysis of health impacts provides the information required to assess the sizeable returns on investment generated through the scale-up of prioritized NCD control and prevention strategies.

See CD for:

- Acknowledgements
- References
- Appendices

Abbreviations

AMI	acute myocardial infarction
CVD	cardiovascular disease
DHS	Demographic and Health Survey
DPAS	Global Strategy on Diet, Physical Activity and Health
HMIS	Health Management Information System
L	litre
mmol	millimole
MoH	Ministry of Health
MPOWER	WHO tobacco control comprehensive implementation programme*
MSH	Management Sciences for Health
NCD	noncommunicable disease
PA	physical activity
UN	United Nations
US	United States
WHO	World Health Organization
WHO PEN	WHO Package of Essential NCD Interventions

* Monitor tobacco use and prevention policies
Protect people from tobacco smoke
Offer help to quit tobacco use
Warn about the dangers of tobacco
Enforce bans on tobacco advertising, promotion and sponsorship
Raise taxes on tobacco

Costing Tool – User Guide

Introduction

For background and methods related to the Costing Tool, see pages 1–14 of the World Health Organization (WHO) document Scaling Up Action against Noncommunicable Diseases: How Much Will It Cost? (a copy is on the compact disc).

Summary: Step-by-step guide for using the noncommunicable diseases (NCDs) Costing Tool

Note: Throughout this worksheet and the rest of the Excel workbook, the blue cells show data that should be checked – and modified as required – by the tool user. Examples include population statistics and coverage rates (SetUp worksheet). Note: you can overwrite the values in these cells if more appropriate/recent data are available. used.

1. Save the file titled "NCDs Costing Tool" on your desktop.

2. Open and read the Costing Tool – User Guide (Word document).

3. Open the NCDs Costing Tool file (Excel file). Read the Introduction worksheet.

4. Click the worksheet tab titled "SetUp":

   ■ Enter your country from the drop-down menu (cell E14). Default demographic, epidemiological and economic data for this country will be automatically populated.

   ■ Choose the desired pattern of scale-up from the drop-down menu – or leave as a default pattern of "exponential growth" (cell E19).

   ■ Select the desired currency from the drop-down menu (cell E21).

   ■ Choose the NCD interventions to be included (column C).

   ■ Specify current and target coverage levels for each of the included interventions (columns K and L for risk factor interventions and columns O and P for primary care interventions).

5. In the worksheet tab titled "Default Values Input":

   ■ For Tables 1–11, review the grey-shaded column "WHO default value" for each table. If you need to change the choice of interventions, coverage or commodities prices given in the tables, make the modification in the blue-shaded column "country value". Then the figure in the adjoining green-shaded column, which is used for calculations, will automatically change. ONLY numerical figures

should be entered in the blue-shaded column. No text is permitted in the blue-shaded column "country value". Indicate the source/reference of the figures/parameters that you have used for the blue-shaded column in the corresponding "source column".

■ If you agree with the WHO default values in the grey-shaded column, do not make any entries in the blue-shaded column; leave it blank. The final value used for calculating costs is shown in the green-shaded column. This column is calculated automatically.

6. Once all data revisions have been completed, view the results in the Summary Results worksheet. Assess implied cost and resource implications of scale-up for feasibility and sustainability.

7. Reconfigure the model to see the impact of different parameter choices, in particular:

■ Addition/removal of certain NCD interventions or conditions.

■ Increase/decrease of target coverage levels for selected interventions.

User's notes

The Costing Tool is intended to provide cost estimates for national scale-up of a set of priority interventions (best buys) for prevention and control of NCDs. This is a core set of interventions prioritized by WHO in 2011, based on cost effectiveness, impact and feasibility of implementation. The best buys comprise population-wide interventions and health system interventions targeting individuals (see page 12, Table 1 in the document Scaling Up Action against Noncommunicable Diseases: How Much Will It Cost?).

The NCDs Costing Tool has a user-friendly format and is pre-filled with country-specific (WHO default) demographic data, epidemiological data, standardized assumptions for disease management based on the WHO protocols of the WHO Package of Essential NCD Interventions (WHO PEN) (for primary care in low-resource settings – the WHO PEN document, protocols and other tools are included on the compact disc) and costs of commodities, etc. The Costing Tool can be used without any additional country-specific data/information; however, the user has the option to amend some of the country-specific data/information (e.g. costs of commodities and human resources), if necessary.

The Costing Tool provides the option to select specific interventions from NCD best buys, the mode of scale-up and the current and target coverage levels of interventions. Table 1 lists the information used in this tool.

If necessary, the WHO default values and standard assumptions may be reviewed and adapted to country contexts. Users have the option to change default values presented in the tool to explore different

options and sensitivities, but the assumptions preferably should be evidence-based country assumptions – and agreed by the Ministry of Health (MoH) and partners – to make the overall exercise reasonable, acceptable and useful.

Purpose of the Costing Tool

The tool is intended for planning national scale-up of prevention and control of NCDs with a focus on best buy interventions for NCDs.

See CD for:

■ Using the Costing Tool

Other tools: (see CD)

Sample clinical record for monitoring WHO PEN interventions

Sample Questionnaire for Rapid Assessment of Capacity of Primary Care Facilities for integration of WHO PEN interventions

Implementation tools

Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings

Why do we need these implementation tools?

- These tools of the WHO Package of Essential Noncommunicable Diseases Interventions (WHO PEN) support implementation of very cost effective interventions through an integrated approach.

- Implementation of WHO PEN is a key component of the objective 4 of the Global Action Plan. These tools will enable early detection and management of cardiovascular diseases, diabetes, chronic respiratory diseases and cancer to prevent life threatening complications (e.g. heart attacks, stroke, kidney failure, amputations, blindness).

- Effective implementation of WHO PEN, combined with other very cost effective population-wide interventions, will help even resource constrained settings to attain the global voluntary targets related to reduction of premature mortality and prevention of heart attacks and strokes.

- Equitable financing of interventions in WHO PEN can be a first step for addressing prevention and control of noncommunicable diseases within the universal health coverage agenda.

World Health Organization

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