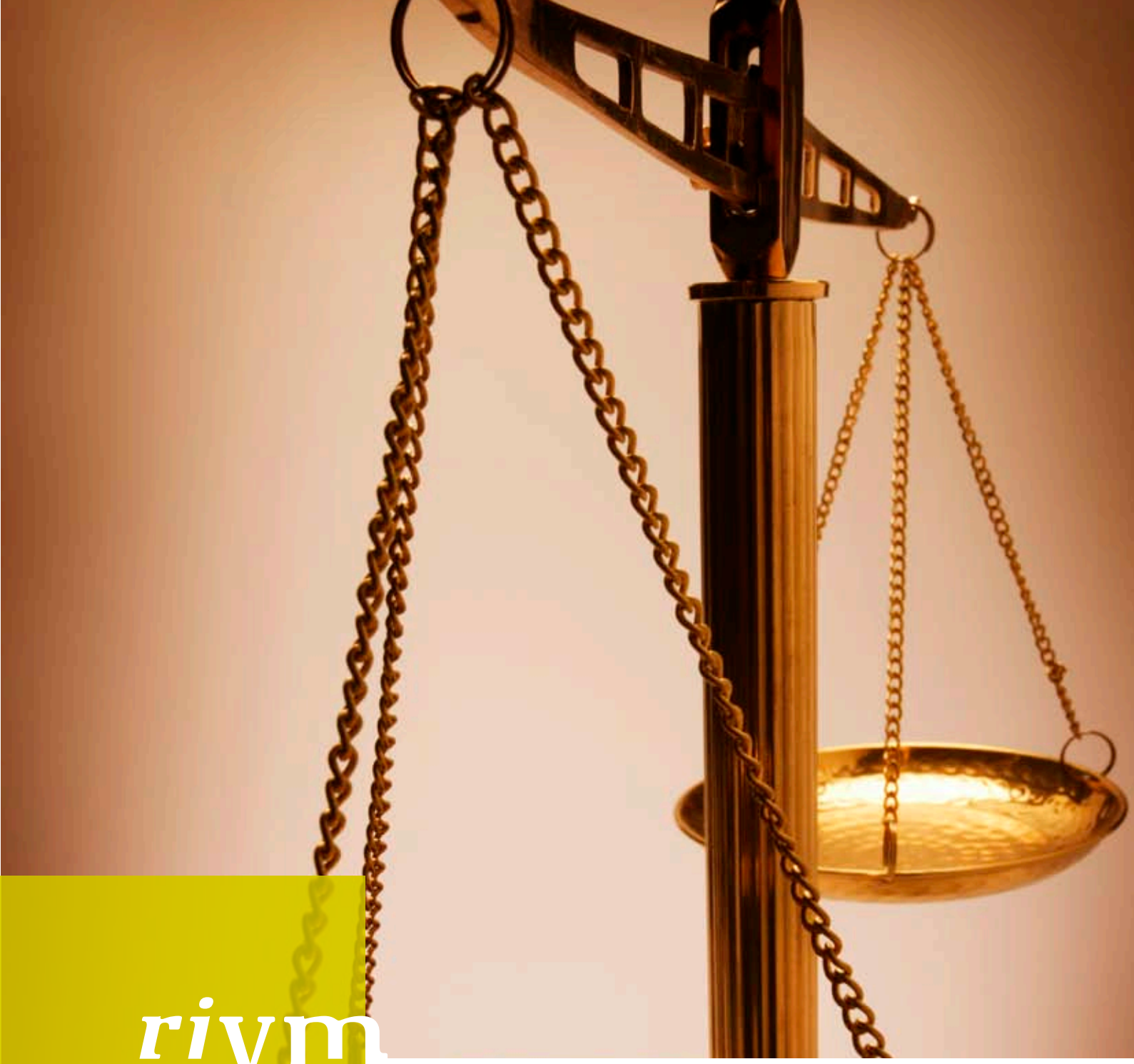

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M. van den Berg | P.F. van Gils | G.A. de Wit | A.J. Schuit

Economic evaluation of prevention

Fourth report on the cost-effectiveness of preventive interventions

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Rapport in het kort

Economische aspecten van preventie
Vierde signaleringsrapport

In dit rapport zijn zeven preventieve maatregelen gesignaleerd die volgens literatuuronderzoek kosteneffectief zijn en in Nederland nog niet landelijk worden aangeboden. Kosteneffectief houdt in dat de kosten relatief laag zijn in verhouding tot de verwachte gezondheidswinst. Meer onderzoek is nodig om te kijken of deze interventies voor Nederland wenselijk zijn. Voor de meeste ontbreekt namelijk overtuigende bewijslast of ze medisch gezien effectief zijn. Bovendien zijn ze niet allemaal eenvoudig te implementeren, bijvoorbeeld omdat mensen terughoudend zijn om zich te laten screenen of vaccineren.

Het gaat om de volgende preventieve maatregelen:

- screening op en behandeling van infectie met Helicobacter pylori om maagaandoeningen te voorkomen;
- vaccinatie van gezonde kinderen tegen griep;
- screening op osteoporose van vrouwen van 70 jaar of ouder door het meten van de botdichtheid;
- preventieve behandeling van mensen met een verhoogd risico op hart- en vaatziekten met aspirine;
- een oefenprogramma voor zelfstandig wonende ouderen om te voorkomen dat ze vallen en valgerelateerde verwondingen oplopen;
- preventieve behandeling van mensen die een hartinfarct hebben doorgemaakt met omega-3 visvetzuren;
- leefstijlinterventie voor mensen met verstoorde glucosetolerantie ter preventie van diabetes mellitus.

In het rapport zijn het gezondheidsprobleem waar de interventie zich op richt, de interventie zelf, de effectiviteit, en de kosteneffectiviteit beschreven. Vervolgens zijn aspecten van vertaalbaarheid van de economische evaluaties naar de Nederlandse situatie en van implementatie van de interventie in Nederland besproken. Dit rapport is het vierde uit een serie van over economische aspecten van preventie en is in samenwerking met ZonMw geschreven.

Trefwoorden: kosteneffectiviteit, economische evaluatie, preventie, vaccinatie, screening, gezondheidsbevordering, literatuuronderzoek

Abstract

Economic evaluation of prevention
Fourth report on the cost-effectiveness of preventive interventions

This report is the fourth in the series of reports that aim to identify cost-effective preventive interventions that have not yet been systematically implemented in the Netherlands. The report is written in close collaboration with ZonMw (the Netherlands Organisation for Health Research and Development). In this report seven new interventions are presented. For all interventions brief information on the preventable disease/health problem is presented, along with information about the intervention, its effectiveness and cost-effectiveness, issues related to transferability of foreign study results to the Dutch setting, and finally, feasibility of implementation in the Netherlands.

The following interventions were included: population screening for *Helicobacter pylori* to prevent dyspepsia, peptic ulcer and gastric cancer, universal influenza vaccination of children, universal bone densitometry screening of women aged 70 years and older, low-dose aspirin in the primary prevention of cardiovascular disease, exercise to prevent falls and fall-related injuries in independently living elderly, N-3 Polyunsaturated Fatty Acids (PUFA) after myocardial infarction, lifestyle intervention to prevent diabetes mellitus.

Two of the seven interventions are lifestyle interventions. The majority of the interventions comes from the field of disease prevention. It should be stressed that only three interventions have a conclusive evidence-base for effectiveness. Contrary to our last report, the transferability of results of foreign studies to the Dutch context was good, except for two interventions. However, there is considerable concern with respect to implementation of these interventions in the Netherlands.

Key words: cost-effectiveness, economic evaluation, prevention, vaccination, screening, health promotion, literature review

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Preface

This report describes the evidence on cost-effectiveness of seven preventive interventions. It is the fourth in a series on cost-effectiveness of prevention. Many RIVM-colleagues and many experts from various universities provided with feed-back on drafts of this report. We would like to thank all of them for their contribution to our work. Furthermore we would like to the staff members of the ZonMw Prevention Program for their work on the assessment of the implementation potential of the seven interventions: Marja Westhoff, Margreet Bloemers, Tonnie Bakkenist, John Krol, and Willem de Regt.

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Summary

Introduction
In many countries, including the Netherlands, economic evaluations play a role in decision making about reimbursement or implementation of a specific intervention. Decision makers and policy makers need information about the effectiveness of an intervention in relation to its costs, to assess if an intervention provides good value for money. In the light of the many new possibilities for prevention, and the limited health care budget, the Ministry of Health, Welfare and Sport asked the RIVM since 2003 to identify preventive interventions, not systematically implemented, that may be cost-effective in reducing the burden of disease in our country. Since then the RIVM has published a series of reports on the cost-effectiveness of preventive interventions. This report is the fourth in the series. An economic evaluation is a comparative analysis of the costs and effects of two or more interventions. Generally, a new intervention is compared to usual care, which can be the standard intervention or no intervention at all. In the context of this series of reports, an intervention is considered cost-effective if three or more economic evaluations conclude that the incremental cost effectiveness ratio (ICER) is around or below € 20.000 per quality adjusted life year (QALY) or life year (LY) gained.

Selection of interventions
To select which interventions to include in the report, a two-step approach was followed. In the first step, a longlist with possible interventions was created. The longlist was based on the longlist of our most recent report in this series added with a systematic search of the economic evaluations of new preventive interventions that were published during the inclusion period (April 2006 – April 2007). In the second step these interventions were evaluated by several criteria to reach a shortlist of interventions. Inclusion criteria were (a) not described in one of the former reports, (b) not systematically implemented in the Netherlands, (c) relevant for the Dutch situation. All available economic evaluations of the pre-selected interventions were analysed on the following criteria: (d) high quality study, (e) comparable scenarios, (f) the base case ICERs were around or below € 20,000. Seven preventive interventions fulfilled all criteria, and were selected for detailed description in the present report. For all included interventions a general appraisal of four aspects (effectiveness, cost-effectiveness, transferability and implementation) was performed using our earlier developed two-star classification system. When an aspect was given one star then the aspect was evaluated relatively unfavourable; when an aspect was awarded with two stars then the aspect was favourably evaluated.

Feasibility of implementation
The potential of implementation of the selected interventions in the Dutch health care system was assessed by staff members of the ZonMw Prevention Program. The selected interventions were compared and checked with ZonMw projects, national reports and advices for health policy, national professional guidelines and expert opinions. Based on this, ZonMw roughly classified the implementation potential using a semi-quantitative method, the so called 'VIS-score', which is based on the Balanced Scorecard. The VIS-score is a 5-point scale to assess the implementation potential on four aspects: (1) innovation, (2) user groups, (3) resources and (4) organization.

Results
Population screening for Helicobacter pylori to prevent dyspepsia, peptic ulcer and gastric cancer
Helicobacter pylori (*H. pylori*) can cause a chronic infection of the gastric wall and is associated with dyspepsia, peptic ulcer, and gastric cancer. In the Netherlands, the incidence of gastric cancer is about 2,000 cases per year, and the incidence of peptic ulcer is estimated at 8,000 cases per year. There are accurate, inexpensive and non-invasive tests for detecting *H. pylori* infection. Eradicating a *H. pylori* infection by triple therapy consisting of two antibiotics and an acid-suppressive drug is effective (80-

90%) too. Currently, only patients with recurrent dyspepsia are tested for *H. pylori.* The new intervention is population screening. We found 6 economic evaluations of *H. pylori* screening in the literature. All studies included only direct costs and concluded that onetime screening of the middle-aged population for *H. pylori* infection and treating infected persons is cost-effective. The ICER ranges from cost-saving to $ 25,000 (2006 €: 29,250) per LY gained. However, since there is no direct evidence that *H. pylori* eradication reduces gastric cancer mortality, assumptions were made regarding the level of this risk reduction. This makes the outcomes of the cost-effectiveness analyses relatively weak. Several factors indicate that the favourable ICERs derived from foreign studies may not be directly transferable to the Dutch situation. So, before a conclusive decision can be made regarding implementation of population screening on *H. pylori* infection in the Netherlands, more research knowledge is required about the fundamental mechanisms of the infection, the resulting diseases, and the efficiency of a population screening compared to case finding according to the current guideline.

Universal influenza vaccination of children
Influenza is an acute respiratory illness, caused by the influenza virus. Symptoms of influenza are: fever, headache, muscle pain, sore throat, and coughing. The incidence in young children is relatively high. In the year 2006/2007, the incidence among children under the age of four was 37 in 1,000. Although universal influenza vaccination of healthy children (e.g. 0.5 to 4 years of age) is implemented in several countries, the evidence base for the effectiveness of vaccinating young children is inconclusive. A considerable amount of recent foreign economic evaluations conclude that if vaccination of all children against influenza is effective it is also cost-effective. The ICER ranges from cost-saving to $ 28,000 (2006 €: 27,160) per LY gained. However, there are doubts about the implementation of universal influenza vaccination in children in the Netherlands, because Dutch parents are rather critical towards vaccination of healthy children against an infection that is generally self-limiting, and uncomplicated. To conclude, more research is needed on the effectiveness of vaccination in young healthy children, the added value of influenza vaccination in relation with the current vaccination against pneumococcal infection, and the acceptance of the vaccination programme by the parents.

Universal bone densitometry screening of women aged 70 years and older
Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Based on the demographic development only, an increase of 37% is expected in the absolute number of women with osteoporosis between 2005 and 2025. The costs of cure and care of osteoporosis in the Netherlands in 2003 were estimated at € 500 million. The present Dutch guidelines on osteoporosis recommend BMD measurement in women with risk factors for osteoporosis. The Dutch Institute for Healthcare Improvement (CBO) recently concluded that the sensitivity of screening all post menopausal women is too low (45%) to support universal screening. Recently, the Dutch Health Council confirmed this and issued a negative advice to the minister of Health concerning screening in GP practices. Until now, no trials have evaluated the effectiveness of screening. Hence the evidence level for effectiveness of screening is relatively poor. Four economic evaluations of screening and treatment of postmenopausal women aged 70 years and older were found in the literature. ICERs ranged from $ 5,600 to $ 72,877 (2006 €: 5,600-69,233). Translation of the ICERs to the Dutch situation will not make them more unfavourable.

Low-dose aspirin in the primary prevention of cardiovascular disease
Coronary heart disease is the leading cause of death in the Netherlands. Aspirin is often used for its analgesic, antipyretic, anti-inflammatory and anti-platelet (blood-diluting) effect. At present the Dutch multidisciplinary CBO guideline ‘Cardiovasculair Risicomanagement’ (Cardiovascular Risk management) describes that there is not enough evidence for a standard treatment with aspirin for people without CHD. Due to the side effects (gastro-intestinal bleeding, haemorrhagic stroke) aspirin is

not suitable for all individuals and therefore they indicate that the advantages do not outweigh the negative effects. On the other hand the European guideline recommends the use low dose aspirin in risk groups. The literature search resulted in five good quality economic evaluations of the use of low-dose aspirin in the primary prevention of cardiovascular disease. These studies showed that among high risk individuals (10-year risk ≥ 10%) aspirin is a cost-effective intervention, taking into account adverse health effects. In four evaluations aspirin treatment was dominant to no aspirin treatment. In one study aspirin treatment was compared with smoking cessation, resulting in an ICER of € 15,799 (2006€:16,431) for moderate risk populations aged 60 years. No major problems are expected with the transferability of the outcomes of the economic evaluations to the Dutch situation. However, physicians may form a barrier by being reluctant to prescribe aspirin, because they are concerned about side effects, and alternative treatments (other drugs and lifestyle programmes) are available.

Exercise to prevent falls and fall-related injuries in independently living elderly
One in three independently living elderly falls at least once per year and almost 70% of in the community dwelling elderly people experience physical consequences from a fall. The international literature shows effectiveness of fall prevention programmes for independently living elderly and supports widespread implementation of a home exercise program. In a meta-analysis it was concluded that the number of falls is about 35% lower in subjects following a prevention programme compared to a control group. There are four studies that evaluated the cost-effectiveness of an exercise program to prevent falls among independently living older people. All studies showed favourable ICERs per fall prevented (range NZ$ 426 to NZ$ 3404; 2006 €: 248 to 2,689). With regard to transferability of the results to the Dutch context we conclude that it is likely that the intervention will be cost-effective in the Netherlands as well. However, from community experiments with fall prevention it appears that there is a lack for continuity if it comes to implementation. Further research is necessary to investigate what factors influence (long-term) compliance with the program.

N-3 Polyunsaturated Fatty Acids (PUFA) after myocardial infarction
In 2004, almost 309,000 patients were hospitalized for coronary vascular disease. Of these 29% (90.000) was due to ischemic coronary heart disease, of which 24,000 were myocardial infarctions (MI). In the Netherlands different guidelines exist in the treatment and prevention of a second MI. None of these include additional dietary supplementation of highly concentrated n-3 polyunsaturated fatty acids (PUFA). Epidemiological studies show that omega-3 fatty acids EPA and DHA may protect against sudden cardiac death, fatal and nonfatal myocardial infarction and cardiac arrhythmias. Some international cardiac societies have incorporated PUFAs (by fish intake) for tertiary prevention into their respective guidelines. Four economic evaluations were found in the literature investigating the use of n-3 PUFA for tertiary prevention after myocardial infarction (MI). The intervention shows favourable cost-effectiveness with ICERs ranging from £2,812 to € 24,603 (2006 € : 4,162 to 31,984). Before practitioners can decide about including recommendations of PUFA supplements in their guidelines, more knowledge is needed with respect to harms and benefits of supplements and preventive mechanisms of PUFA. Furthermore a change of culture and attitude among policy makers and caregivers is required before recommendation on supplements can be implemented.

Lifestyle intervention to prevent diabetes mellitus
In 2003 almost 600.000 people had diabetes mellitus in the Netherlands. Based on demographic development an increase in the absolute total number of persons with diabetes mellitus of 32.5% between 2005 and 2025 is expected. Impaired Glucose Tolerance (IGT) is the preliminary stage of diabetes mellitus. The main risk factors of IGT are overweight/obesity and lack of physical activity. At present the GP guideline for prevention of diabetes recommends that IGT-patients should be advised to stop smoking, increase their physical activity, eat a healthy diet and loose weight if the body mass index ≥ 25 kg/m². However, no lifestyle intervention is offered. Large intervention studies demonstrated that intensive lifestyle interventions reduce the incidence of diabetes compared with a

placebo intervention. The international health economic literature shows that life-style programs preventing diabetes mellitus are cost-effective. A Dutch economic evaluation presents an ICER for the community intervention (compared with no prevention) between € 3,900-3,100 (2006€: 3,939-3,131) and for the health care intervention between € 5,500-3,900 (2006 €: 5,555-3,939). Evidence based lifestyle interventions (exercise plus diet) are highly feasible in the Netherlands. In their report 'Rechtvaardige en duurzame zorg' (Fair and sustainable healthcare), the Council for Public Health and Health Care (Raad voor de Volksgezondheid en Zorg, RVZ) recommends to reimburse life-style programs in the prevention of diabetes mellitus.

Discussion

We included seven preventive interventions in this report that have favourable cost-effectiveness ratios, and are not systematically implemented in the Netherlands. Two interventions are lifestyle interventions, five of them fall in the domain of disease prevention. It should be stressed that this proportion reflects the lack of economic evaluations in the domain of health promotion and health protection. It can not be concluded that interventions in these domains are generally less cost-effective. It should also be noted that only three of the seven interventions have a conclusive evidence-base for effectiveness. This remarkable finding suggests that the absence of a convincing evidence-base for effectiveness does not put restrains on modelling potential cost-effectiveness of such an intervention. Contrary to our last report, the transferability of results of foreign studies to the Dutch context was good, except for two interventions. However, there is considerable concern with respect to implementation of these interventions in the Netherlands.

Table: (Cost)-effectiveness, transferability and implementation potential of included interventions[1]

Intervention	Effectiveness	Cost-effectiveness	Transferability	Implementation
H. pylori screening	*	*	*	*
Influenza vaccination	*	*	**	*
Osteoporosis screening	*	*	*	*
Aspirin use to prevent CVD	**	**	**	*
Exercise to prevent falls	**	**	**	*
PUFAs to prevent recurrent MI	*	*	**	*
Lifestyle interv. to prevent DM2	**	**	**	**

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

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Samenvatting

Inleiding
In veel landen, waaronder Nederland, spelen economische evaluaties een rol in de besluitvorming over vergoeding of invoering van een bepaalde behandeling of interventie. Hiervoor is informatie over de effecten van een interventie in relatie tot de kosten ervan noodzakelijk. Een economische evaluatie (of: kosteneffectiviteitsanalyse, KEA) biedt deze informatie. Een KEA is een vergelijkende analyse van de kosten en effecten van twee (of meer) interventies. In het algemeen wordt een nieuwe interventie vergeleken met de gebruikelijk zorg op dat gebied. In de context van deze serie rapporten wordt een interventie als kosteneffectief beschouwd als ten minste drie economische evaluaties concluderen dat de kosteneffectiviteitratio rond of onder de € 20.000 per (voor kwaliteit gecorrigeerd) gewonnen levensjaar ligt.

In 2003 vroeg het ministerie van VWS het RIVM om op regelmatige basis preventie-interventies te signaleren die nog niet in Nederland zijn ingevoerd en die in de wetenschappelijke literatuur als kosteneffectief naar voren komen. Dit rapport is het vierde in deze serie signaleringsrapporten over de kosteneffectiviteit van preventieve interventies.

Selectie van de interventies
De selectie van interventies vond plaats in twee stappen. In de eerste plaats werd een longlist met mogelijke interventies gecreëerd. Deze lijst was gebaseerd op de longlist van het meeste recente rapport uit deze serie, aangevuld met interventies waarvoor in de periode april 2006- april 2007 een eerste economische evaluatie verscheen. Vervolgens werden de interventies op de longlist getoetst aan de hand van een aantal inclusiecriteria: (a) niet eerder beschreven in deze serie, (b) niet systematisch ingevoerd in Nederland, (c) relevant voor de Nederlandse situatie. Voor de beschikbare economische evaluaties van deze interventies golden de volgende aanvullende criteria: (d) kwalitatief goede studie, (e) vergelijkbare scenario's, (f) de kosteneffectiviteitratio's waren op of rond de € 20.000.

Zeven preventieve interventies voldeden aan alle criteria en werden geselecteerd voor gedetailleerde beschrijving in dit rapport. Voor deze interventies werden de volgende aspecten beoordeeld effectiviteit, kosteneffectiviteit, vertaalbaarheid, en implementatie. Hiervoor werd gebruikgemaakt van de eerder ontwikkelde sterrenclassificering: een aspect kreeg één ster als het aspect relatief ongunstig werd beoordeeld en twee sterren als het aspect gunstig werd beoordeeld.

Implementatiepotentieel
Het implementatiepotentieel van de geselecteerde interventies werd beoordeeld door stafmedewerkers van het preventieprogramma van ZonMw. Er werd gebruik gemaakt van gegevens uit: ZonMw-projecten, nationale rapporten en adviezen, richtlijnen, en expertmeningen. Op basis hiervan werd het implementatiepotenteieel beoordeeld aan de hand van een semikwantitatieve methode, de zogenoemde 'VIS-score' (gebaseerd op de *balanced scorecard*). De volgende vier aspecten worden gescoord op een vijfpuntsschaal: (1) innovatie, (2) gebruikersgroepen, (3) middelen en (4) organisatie.

Resultaten
Screening op en behandeling van infectie met Helicobacter pylori ter preventie van maagaandoeningen
Helicobacter pylori (*H. pylori*) kan een chronische infectie van de maagwand veroorzaken en leiden tot maagklachten, maagzweren en maagkanker. In Nederland is de incidentie van maagkanker ongeveer 2000 gevallen per jaar en de incidentie van maagzweren ongeveer 8000 gevallen per jaar. Er zijn goede, goedkope, niet-invasieve tests beschikbaar voor het detecteren van een *H. pylori*-infectie. Eradicatie van een *H. pylori*-infectie middels tripeltherapie (twee antibiotica en één zuurremmer) is effectief. Volgens de CBO-richtlijn 'Maagklachten' moeten alleen mensen met recidiverende

maagklachten getest worden op *H. pylori.* De interventie die in dit hoofdstuk besproken wordt, is screening van (een leeftijdsgroep) de algemene bevolking. In de literatuur werden zes economische evaluaties van zo'n screeningsprogramma gevonden. Alle studies werden gedaan vanuit het gezondheidszorgperspectief en concluderen dat eenmalige screening op middelbare leeftijd op infectie met *H. pylori* kosteneffectief is. De kosteneffectiviteitratio varieerde van kostenbesparend tot $ 25.000 (2006 €: 29.250) per gewonnen levensjaar. Echter, aangezien er geen direct bewijs is dat screening de sterfte aan maagkanker reduceert, berusten de modelberekeningen op aannames voor wat betreft de hoogte van de risicoreductie door screening en behandeling. Bovendien is de vertaalbaarheid van de gunstige studieresultaten naar de Nederlandse situatie beperkt. Een conclusie over de implementatie van een screeningsprogramma kan dus pas getrokken worden als er meer duidelijkheid is over de (lange termijn) effecten van screening en eradicatie, en de relatieve kosteneffectiviteit van populatiescreening ten opzichte van casefinding volgens de huidige richtlijnen.

Vaccinatie van gezonde kinderen tegen influenza
Griep is een acute aandoening van de luchtwegen en wordt veroorzaakt door het influenzavirus. Symptomen zijn onder andere: hoofdpijn, spierpijn, keelpijn en hoesten. De incidentie in jonge kinderen is relatief hoog. In het jaar 2006/2007 was de totale incidentie 12 op 1000, maar de incidentie in kinderen jonger dan vier was 37 op 1000. Hoewel universele vaccinatie van gezonde kinderen in verschillende landen is ingevoerd, is de *evidence base* voor de effectiviteit van het vaccineren van jonge kinderen zwak. Zes ecomische evaluaties concluderen dat – onder de aanname van effectiviteit – vaccineren van alle kinderen tegen influenza kosteneffectief is. De kosteneffectiviteit varieert van kostenbesparend tot $ 28.000 (2006 €: 27.160) per gewonnen levensjaar. Wat betreft de eventuele implementatie van het vaccineren van alle jonge kinderen tegen griep: Nederlandse ouders zijn over het algemeen kritisch tegenover het vaccineren van gezonde kinderen tegen een ziekte die men als niet ernstig ervaart (die meestal ongecompliceerd verloopt en vanzelf weer overgaat). Er is meer onderzoek nodig naar: de effectiviteit van vaccinatie in gezonde jonge kinderen, de toegevoegde waarde van vaccinatie tegen influenza naar vaccinatie tegen pneumokokken, en de acceptatie van zo'n vaccinatie door ouders.

Screening op osteoporose van vrouwen van 70 jaar of ouder middels botdichtheidsmeting.
Osteoporose wordt gedefinieerd als een systemische aandoening van het skelet gekarakteriseerd door een lage botmassa en verslechtering van de microarchitectuur, met als gevolg een toegenomen risico op fracturen. Op grond van demografische ontwikkelingen, wordt een toename van het absolute aantal vrouwen met osteoporose van 37% verwacht tussen 2005 en 2025. De kosten van de behandeling en zorg van osteoporose in Nederland werden in 2003 geschat op € 5 miljoen. De huidige Nederlandse CBO-richtlijn en de richtlijn van het Nederlands Huisartsen Genootschap bevelen een botdichtheidmeting aan voor vrouwen met osteoporoserisicofactoren. Recent stelde het CBO vast dat de sensitiviteit om alle vrouwen na de menopauze te screenen te laag is (45%) om een universele screening te ondersteunen. Onlangs bevestigde de Gezondheidsraad dit en gaf een negatief advies aan de minister van VWS betreffende screening in huisartsenpraktijken. Tot nu toe zijn er géén onderzoeken die de effectiviteit aantonen. Vandaar dat het evidentieniveau voor de effectiviteit relatief laag is. Vier economische evaluaties betreffende onderzoek en behandeling van vrouwen van 70 jaar en ouder werden gevonden in de literatuur. De kosteneffectiviteitratio's varieerden van $5.600 tot $ 72.000 (2006 €: 5.600-69.233). De vertaling van deze ratio's naar de Nederlandse situatie zal hen niet ongunstig beïnvloeden.

Preventieve behandeling van mensen met een verhoogd risico op hart- en vaatziekten met aspirine
CHD is de belangrijkste doodsoorzaak in Nederland. Aspirine wordt vaak gebruikt ter pijnstilling, koortsremming, als ontstekingsremmer en als bloedverdunner. Op dit moment beschrijft de multidisciplinaire CBO-richtlijn 'Cardiovasculair Risicomanagement dat er onvoldoende bewijs is voor een standaardbehandeling met aspirine voor mensen zonder CHD. Vanwege de neveneffecten (gastro-

intestinale bloeding en hersenbloeding) is aspirine niet geschikt voor iedereen en daarom wordt aangegeven dat de voordelen niet opwegen tegen de nadelen. Aan de andere kant, de Europese richtlijn beveelt het gebruik van een lage dosis aspirine aan in risicogroepen. Het literatuuronderzoek resulteerde in vijf kwalitatief goede economische evaluaties over het gebruik van een lage dosis aspirine als primaire preventie van cardiovasculaire ziekten. Deze studies toonden aan, dat onder individuen met een verhoogd risico (10-jaars risico ≥ 10%), aspirine een kosteneffectieve interventie is, rekening houdend met nadelige effecten. In vier evaluaties was aspirinebehandeling dominant vergeleken met géén aspirinebehandeling. In één studie werd aspirinebehandeling vergeleken met stoppen met roken, resulterend in een kosteneffectiviteitratio van $15.799 (2006 €: 16.431), voor een populatie met gematigd risico van 60 jaar. Er worden géén grote problemen verwacht met de vertaling van de resultaten uit de economische evaluaties naar de Nederlandse situatie. Nochtans kunnen artsen een barrière vormen doordat zij aarzelen met het voorschrijven van aspirine, omdat zij bezorgd over de neveneffecten en er andere behandelingen (andere medicatie en leefstijl programma's) beschikbaar zijn.

Oefenprogramma voor zelfstandig wonende ouderen ter preventie van vallen en valgerelateerde verwondingen
Eén op de drie thuiswonende oudere valt minstens één keer per jaar en bijna 70% van de zelfstandig wonenden ondervindt lichamelijke gevolgen van een val. De internationale literatuur toont de effectiviteit van valpreventieprogramma's voor zelfstandig wonende ouderen en ondersteunt een uitgebreide implementatie van een thuisoefenprogramma, In een meta-analyse was de conclusie dat het aantal valincidenten met 35% vermindert bij mensen die een preventieprogramma volgen in vergelijking met diegenen die een dergelijk programma niet volgen. Er zijn vier economische evaluaties gevonden die de kosteneffectiviteit beoordeelden van oefenprogramma's ter preventie het vallen van zelfstandig wonende ouderen. Alle studies toonden gunstige kosteneffectiviteitratio's per voorkomen val (van NZ$ 426 tot NZ$ 3,404; 2006€: 248 tot 2.689). Met betrekking tot de vertaalbaarheid van de resultaten naar de Nederlandse situatie concluderen wij dat verwacht mag worden dat de interventie ook in Nederland kosteneffectief is. Nochtans blijkt dat experimenten in de populatie aantonen, dat er bij implementatie een gebrek aan continuïteit bestaat. Verder onderzoek is noodzakelijk om vast te stellen welke factoren de deelnamebereidheid beïnvloeden.

Preventieve behandeling van mensen die een hartinfarct hebben doorgemaakt met omega 3 visvetzuren.
In 2004 werden bijna 309.000 patiënten in het ziekenhuis opgenomen met een coronaire vasculaire ziekte. Van dit aantal was 29% (90.000) toe te schrijven aan een ischaemische coronaire ziekte, waarvan 24.000 een acuut hartinfarct. In Nederland bestaan er verschillende richtlijnen voor de behandeling van een hartinfarct en voor de preventie van een nieuw infarct. Géén hiervan omvat toevoeging van geconcentreerd n-3 meervoudig onverzadigde vetzuren (PUFA) aan de bestaande medicatie. Epidemiologische studies tonen aan dat de omega-3 vetzuren EPA en DHA een bescherming kunnen bieden tegen plotselinge hartdood, een acuut hartinfarct en ritmestoornissen. Sommige internationale verenigingen voor cardiologie hebben PUFA's (via visconsumptie) opgenomen in hun richtlijnen. Er werden vier economische evaluaties gevonden in het literatuuronderzoek naar de toepassing van n-3 PUFA in de tertiaire preventie van een hartinfarct. De interventie toont een gunstige kosteneffectiviteit met een kosteneffectiviteit ratio van £2.812 tot €24,603 (2006 €: 4.162 tot 31.984). Voordat cardiologen kunnen overgaan tot het aanbevelen van PUFA-supplementen in de richtlijnen, is meer kennis nodig omtrent de voordelen en nadelen en de preventieve werking van PUFA. Verder is er een verandering nodig in de cultuur en de houding van beleidmakers en zorgverleners, voordat het aanbevelen van supplementen kan worden geïmplementeerd.

Leefstijlinterventie voor mensen met verstoorde glucosetolerantie ter preventie van diabetes mellitus.
In 2003 hadden bijna 600.000 mensen in Nederland diabetes mellitus. Gebaseerd op demografische

ontwikkelingen wordt tussen 2005 en 2025 een verhoging van het absolute aantal mensen met diabetes mellitus verwacht van 32,5%. Verstoorde glucosetolerantie (IGT) is voorstadium van diabetes mellitus. De belangrijkste risicofactoren voor IGT zijn overgewicht/obesitas en gebrek aan lichamelijke activiteit. Op dit moment wordt in de richtlijn van het Nederlands Huisartsen Genootschap geadviseerd aan IGT-patiënten, ter preventie van diabetes , te stoppen met roken, de fysieke activiteit te verhogen, gezond te eten en af te vallen indien de body mass index hoger is dan 25 kg/m². Op dit moment wordt er géén leefstijlinterventie aangeboden. Grote interventiestudies toonden een reductie van diabetes met een leefstijlinterventie vergeleken met een placebo-interventie. De internationale gezondheidseconomische literatuur toont aan dat leefstijlprogramma's ter preventie van diabetes kosteneffectief zijn. Een Nederlandse economische evaluatie geeft een kosteneffectiviteitratio voor een populatie-interventie (vergeleken met géén interventie) tussen €3900 en 3100 (2006 €: 3939-3131 en voor een interventie gericht op alleen de risicogroep tussen €5500-3900 (2006 €: 5555-3939). Op evidentie gebaseerde leefstijlinterventies (oefeningen en dieet) zijn zeer goed uitvoerbaar in Nederland. In hun rapport 'Rechtvaardige en duurzame zorg' adviseert de Raad voor de Volksgezondheid en Zorg (RVZ) leefstijlprogramma's ter preventie van diabetes mellitus te vergoeden vanuit de zorgverzekering.

Discussie

In dit rapport worden zeven niet in Nederland ingevoerde preventieve interventies met gunstige kosteneffectiviteit beschreven. Twee interventies zijn leefstijlprogramma's en vijf interventies vallen in het domein van de ziektepreventie. Er werden geen interventies uit het domein van de gezondheidsbescherming geïncludeerd. Het moet benadrukt worden dat deze verdeling de beperkte beschikbaarheid van economische evaluaties van gezondheidsbevorderende en gezondheidsbeschermende maatregelen weerspiegelt en dat *niet* geconcludeerd kan worden dat interventies in deze domeinen over het algemeen minder kosteneffectief zijn.

Voor slechts drie van de zeven interventies was voldoende bewijslast voor de effectiviteit van de interventie beschikbaar. Het ontbreken van overtuigende effectiviteitgegevens weerhoudt onderzoekers er niet van om de potentiële kosteneffectiviteit van zo'n interventie te berekenen. In tegenstelling tot het vorige signaleringsrapport is nu voor de meerderheid van de interventies geconcludeerd dat de kosteneffectiviteitratio's wel vertaalbaar zijn naar de Nederlandse context. Ten slotte, voor op één na alle interventies is het implementatiepotentieel zeer beperkt.

Tabel: Effectiviteit, kosteneffectiviteit, vertaalbaarheid en implementatiepotentieel van de beschreven interventies [1]

Interventie	Effectiviteit	Kosteneffectiviteit	Vertaalbaarheid	Implementatie
H. pylori screening	*	*	*	*
Influenza vaccinatie	*	*	**	*
Osteoporose screening	*	*	*	*
Aspirine ter preventie van HVZ	**	**	**	*
Oefenprogramma tegen vallen	**	**	**	*
Visvetten tegen terugkerend HI	*	*	**	*
Leefstijlprogr. ter prev. van DMII	**	**	**	**

[1] één ster: beperkt bewijs/ongunstig, twee sterren: sterk bewijs/gunstig

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1 Introduction

1.1 Prevention

Prevention is a comprehensive concept that can be distinguished into three forms of preventive actions: health protection, health promotion, and disease prevention. Health protection interventions reduce health risks by changing the physical or social environment. It includes provisions such as sewer systems, safe drinking water supplies, regulating exposure to hazardous substances, flood defences, road and food safety provisions, and building regulations. Regulating such matters is generally regarded as part of the collective responsibilities of governments and to a large extent falls outside the health care domain. Health promotion normally involves action to encourage healthy behaviour or to discourage unhealthy behaviours. This includes the establishment of a healthy social and physical environment that supports a healthy lifestyle. Health promotion interventions frequently take the form of public information campaigns focused on the general population or on certain population groups. Disease prevention concerns actions to prevent the occurrence of a specific disease (e.g. by vaccination) or to detect (a predisposition towards) a disease in an early stage (screening) (De Hollander et al., 2007; De Wit et al., 2007).

An increasing number of preventive interventions are coming available for an increasing number of diseases, disorders, and health complaints. Accordingly, in the Netherlands, an increasing number of preventive interventions are being offered to the public. The Dutch public health information portal (National Compass on Public Health, www.nationaalkompas.nl), provides an extensive overview of current preventive interventions or programs, subdivided into different target groups and settings. Scientific research and technological advance continuously generate new possibilities for prevention. This includes new preventive interventions as well as new developments in existing prevention. Since ‘an ounce of prevention is worth a pound of cure’, prevention receives more and more attention.

The increasing interest in prevention is reflected by the exponentially increasing number of studies on prevention in the scientific literature. This can be illustrated by a general search in Medline (mid-2007), which yielded over 850,000 studies utilizing the text word ‘prevention’. As shown in Figure 1, not only the absolute number of prevention studies is increasing, also the relative number increases (relative to the total amount of Medline indexed studies, which was over 17 million studies in the summer of 2007). Currently, more than one in 15 studies in Medline mentions any form of prevention (compared to one in 30 in the 1970s).

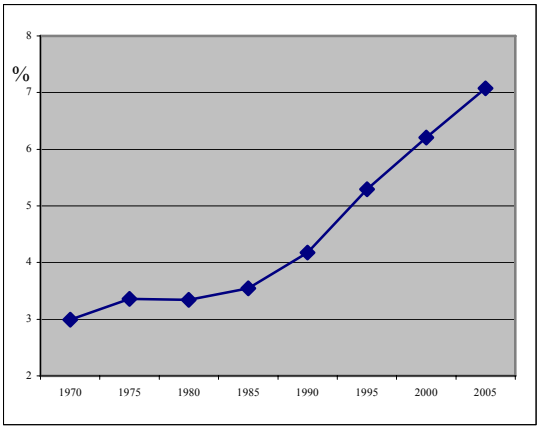

Figure 1: Relative number of new prevention studies compared to the total number of Medline-studies per five years

1.2 Effectiveness and cost-effectiveness

Before an intervention may be implemented, a firm evidence base for its effectiveness is needed. The effects of an intervention should be both statistically and clinically significant. The highest level of evidence is obtained when effectiveness is determined in one or more high quality randomized controlled trials (RCTs) (CBO, 2007). However, in light of increasing health care costs and limited resources, an intervention should not only be effective, but efficient or cost-effective too. Nowadays, decision makers and policy makers require information about the effectiveness of an intervention *in relation to* its costs. The question to answer is: does the intervention provide good value for money?

Economic evaluations provide the information needed to answer this question. An economic evaluation is a comparative analysis of the costs and effects of two or more interventions (Drummond et al., 2005). Generally, a new intervention is compared to usual care, which can be the standard intervention or no intervention at all. The outcome of an economic evaluation is expressed as a ratio of costs in relation to effects:

$$\frac{C_{new} - C_{usual\ care}}{E_{new} - E_{usual\ care}}$$

This ratio is called incremental cost-effectiveness ratio (ICER): the difference in costs between the new and the old intervention is divided by the difference in effects between the new and old intervention. Examples of ICERs are: costs per myocardial infarction prevented, and costs per life year (LY) gained. If a new intervention is more effective and less costly than the comparator (the old intervention, or no intervention), than the intervention is 'dominant' to the comparator. If an intervention is less effective and more costly, than it is 'dominated' by the comparator. However, in most cases the new intervention is more effective and more costly than the comparator. That puts up the question: what are the incremental costs to reach the incremental effects?

There are different forms of economic evaluation: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). These three approaches differ in the way in which the effects of an intervention are measured. In a CEA, the effects are measured in the most appropriate natural or physical unit (e.g. cases prevented, or LY gained). In a CUA, the effects of an intervention

are measured in a generalized unit: the number of quality adjusted life years (QALYs) gained. A QALY is a combination of both quantitative effects (number of LY gained) and qualitative effects (quality of life (QOL)) of an intervention. In other words, effects on mortality and morbidity are combined into a single measure. By using this generic measure, the effects and cost-effectiveness of different interventions become comparable. This is why CUA is the recommended form of economic evaluation in many guidelines (CVZ, 2006). However, only a small minority of the published economic evaluation are CUAs (Figure 2). Currently, about 50,000 studies on cost-effectiveness (text words: 'cost-effectiveness', 'cost-utility', or 'cost-benefit') have been published (Medline, summer 2007). Overall, only a small fraction (less than 8%) of these are CUAs. However this fraction is increasing exponentially (Figure 2), indicating that the CUA is becoming the standard method of economic evaluation. Nevertheless, the vast majority of economic evaluations still are CEAs. In a CBA, all costs and effects of an intervention are measured in monetary units. In this approach, effects such as cases prevented or LY gained have to be translated into monetary benefits. Since it is complicated and controversial to value all health effects on an intervention in monetary units, full CBAs are scarce in medical literature.

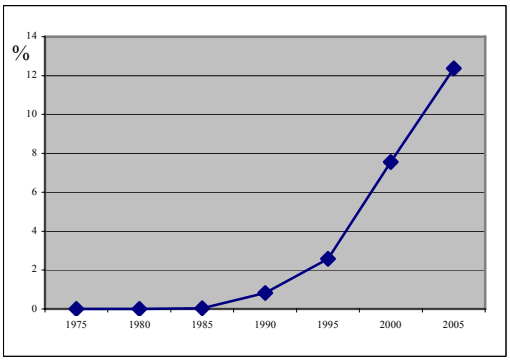

Figure 2: Relative number of cost-utility analyses compared to the total number of economic evaluations per five years

Economic evaluations can take different perspectives. An economic evaluation from the health care perspective takes into account only the health care costs. A broader perspective is the societal perspective in which all relevant costs (and effects) are taken into account (including travel costs, productivity losses, etc.). Although most guidelines recommend to use the societal perspective, the majority of the published economic evaluations use the health care perspective.

Once the ICER of a new intervention is calculated, the next question to answer is: when is an intervention considered to be cost-effective? In other words: when does an intervention present good value for money? The answer on these questions depends on the cost-effectiveness threshold that is used. In different countries, different thresholds are being used. In the UK, for instance, the National Institute for Clinical Excellence and Public Health (NICE) uses a threshold value of £ 20.000 - £ 30.000 (~ € 30.000 - € 45.000) per QALY (Buxton, 2006). In the Netherlands, a frequently cited threshold value is € 20.000 per QALY (Pomp et al., 2007; Casparie et al., 1998). However, it is argued that this threshold is too low and does not reflect societal preferences (Pomp et al., 2007). In fact, reimbursement decisions about e.g. cancer drugs indicate that the actual threshold for medical care indeed is higher than € 20.000 per QALY. Recently, the Council for Public Health and Health care (Raad voor de Volksgezondheid en Zorg, RVZ) proposed a variable threshold, depending on the severity of the disease (RVZ, 2006). The maximum value for this threshold was € 80.000 per QALY.

In many countries, including the Netherlands, cost-effectiveness information does play a role in decision making about reimbursement or implementation of a specific intervention, however often not an explicit, formal role (Pomp et al., 2007). For example, in the Netherlands, only for new extramural drugs a cost-effectiveness analysis is required. The Dutch Health Care Insurance Board (College voor Zorgverzekeringen, CVZ) does however not use an explicit threshold value in their reimbursement judgements.

1.3 Background of the research

In 2003, the Ministry of Health, Welfare and Sports has asked the RIVM to identify preventive interventions, not yet systematically implemented, that may be cost-effective in reducing the burden of disease in our country. Since then the RIVM has published a series of reports on the cost-effectiveness of preventive interventions (Dirkmaat et al., 2003; De Wit et al., 2007; Vijgen et al., 2005). Table 1 shows the interventions that were presented in the two most recent reports (Vijgen et al., 2005; De Wit et al., 2007). The table shows that over 20 interventions (of which several interventions were implemented last years, or are currently being implemented) were identified of which most were vaccinations or screening programs. The present report is the fourth in this series.

Table 1: Preventive interventions that were identified in two earlier reports in this series

Domain	Disease	Intervention	Target group
Disease prevention	Varicella	Vaccination	Children
	Pneumococcal infections	Vaccination	Elderly
	Influenza	Vaccination	Employees
	Hepatitis B	Vaccination	Newborns/adolescents
	Rotavirus	Vaccination	Newborns
	Pertussis	Vaccination	Adolescents
	HPV	Vaccination	Adolescents
	Chlamydia	Screening	Adolescents
	Abdominal aneurysm of aorta	Screening	Male elderly
	Retinopathy	Screening	Diabetes mellitus
	Cervical cancer	Screening (HPV + smear)	Women (30-60)
	Neonatal group beta streptococcal infections	Screening (combination strategy)	Pregnant women
	Obesitas-related diseases	Pharmacological treatment	Obese adults
	Sudden cardiac death	Automatic external defibrillators	General population
	Hip fractures	External hip protectors	Elderly
	Recurrent myocardial infarction	Heart revalidation	Patient with myocardial infarction
	Recurrent depression	Cognitive behavioural therapy	Patients with depression
Health promotion	Smoking-related diseases	Cessation advices by GP	Smoking adults
Health protection	Neural tube defects	Food fortification with folic acid	General population
	Caries	Fluoridation of drinking water	General population
	Head injuries	Bicycle helmets	Children

1.4 Aim of the research

The aim of research that is presented in this report is to identify preventive interventions that are not yet systematically implemented in the Netherlands, and that show favourable cost-effectiveness in at least three good quality economic evaluations. Both new interventions and new developments in existing preventive interventions or programs are included in the report.

2 Methods

2.1 Selection of interventions

To select the interventions, a two-step approach was followed. In the first step, a longlist with possible interventions was created. In the second step, the interventions on the longlist were evaluated by several criteria to achieve a shortlist of interventions.

Longlist
To identify preventive interventions with favourable cost-effectiveness in at least three economic evaluations, we created a longlist of interventions. This longlist was based on:

1. the remaining longlist of our most recent report in this series (De Wit et al., 2007),
2. a systematic search of the economic evaluations of new preventive interventions that were published during the inclusion period (April 2006 – April 2007).

We performed a bottom up search in Medline (up to and including April 2007) for those interventions on the longlist of our previous report (De Wit et al., 2007), that did not have three or more economic evaluations available at that time. The search strategy was similar to the one used in the former reports (De Wit et al., 2007; Vijgen et al., 2005). If we found one or more new economic evaluations of one of these interventions, a description of the intervention, and hyperlinks to the specific papers were included in an Excel-database. Secondly, every economic evaluation of a new intervention that was published during the inclusion period (April 2006 – April 2007), and that was not yet on the longlist, was also included in this Excel-database. To identify *other* economic evaluations of these interventions that were new on the longlist, a bottom up search in Medline for these interventions was performed too. These two searches together resulted in a longlist of new preventive interventions with one or more published economic evaluations.

Shortlist
The next step was to examine only those interventions on the longlist with three or more published economic evaluations. Further inclusion criteria for these *interventions* were

1. not described in one of the former reports
2. not systematically implemented in the Netherlands
3. relevant for the Dutch situation

Those interventions that fulfilled these criteria were included in the pre-selection. Finally, all available *economic evaluations* of the pre-selected interventions were analysed on the following criteria:

1. high quality study (using the criteria as specified by Drummond and Jefferson. (Drummond & Jefferson, 1996)),
2. comparable economic evaluations (e.g. the same intervention and reference scenario),
3. the base case ICERs were around or below € 20,000 per (QA)LY.

Seven preventive interventions fulfilled all criteria, and were selected for detailed description in the present report.

2.2 Description of the interventions

For each intervention the following aspects will be described:

- disease or health problem at which the preventive intervention is aimed,
- current situation concerning prevention of this disease,
- new intervention,
- effectiveness of the intervention,
- cost-effectiveness of the intervention,
- transferability of the results to the Dutch situation,
- implementation potential of the intervention,
- conclusion.

Every chapter was reviewed by one or more RIVM-experts and/or external experts at the specific intervention (see Appendix 1).

2.3 Cost-effectiveness

For a detailed description of how the criterion for cost-effectiveness was made operational, we refer to the report of De Wit et al. (2007). If the ICER an intervention was around or below € 20.000 per QALY (or LY) gained in three or more economic evaluations, than the intervention was included in the study. Nevertheless, detailed investigation of the available studies showed that some ICERs were very sensitive to specific assumptions or contained very broad confidence intervals. So there was still room for a distinction between strong and moderate evidence for the cost-effectiveness of the interventions. Since only a minority of studies presented costs per QALY, different outcome parameters were used. This however made it impossible to calculate one average ICER per intervention, and we could only make a general judgment on the level of cost-effectiveness evidence (strong or moderate).

Because the studies were performed in different countries and in different years, all ICERs were recalculated into 2006-euros. First, the local currencies were recalculated to the value of the euro during the price year of the study, stated by the Organisation for Economic Cooperation and Development (OECD, 2007). Next, these euro values were indexed according to the price index from the Central Office for Statistics (Centraal Bureau voor de Statistiek) (CBS, 2007). When in a study no price year was mentioned, the price year was assumed to be two years before the year of publication.

2.4 Transferability

Since the vast majority of the included economic evaluations were foreign studies, the presented ICERs in the articles could not automatically be transferred or translated to the Dutch situation. Therefore, the results of the selected interventions were assessed on the transferability of the cost-effectiveness evidence to the Dutch situation. Based on a paper of Welte and collegues, the following items were evaluated for possible differences between the country in which the foreign study was performed and the Dutch context (Welte et al., 2004):

- incidence/prevalence of the disease/health problem,
- health care costs,
- practice variation.

These three items, if relevant for the specific intervention, will be discussed in the transferability paragraphs of the seven interventions.

2.5 Implementation

Assessment of implementation potential by the Netherlands Organisation for Health Research and Development (ZonMw)
The potential to implement the selected interventions in the Dutch health care system, has been assessed by staff members of the ZonMw Prevention Programme. The selected interventions were compared and checked with ZonMw projects, national reports and advices for health policy, national professional guidelines and expert opinions. Together, these information sources give insight into opportunities and barriers for implementation of the interventions in the Netherlands. The ZonMw projects show practical information about e.g. the user groups, and organisational aspects. The policy documents provide a framework (e.g. medical, legal and ethical limits) within which a new intervention must fit. As such they are important for health policy makers to decide about implementation and to make resources available.

In addition, ZonMw has made a rough impression of the implementation potential at the present moment by using a semi-quantitative method, the so called 'VIS-score' (Vis, 2004), which is based on the Balanced Scorecard. The VIS-score is a 5-point scale to assess the implementation potential on each of four aspects:

1. innovation (added value, readiness of the intervention for implementation),
2. user groups (access, commitment and experience with the intervention, acceptance),
3. resources (especially financial, its availability for implementation, and structural application),
4. organisation (infrastructure, available capacity for application).

The interpretations of the possible scores on the four dimensions are listed in Appendix 2. The VIS-score was developed at ZonMw and tested for a number of innovations resulting from various programmes. It was found to be a useful instrument to measure the phase of implementation at a given moment, or its progress in time. However, it must be noted that the VIS-score has not been scientifically validated. The selected interventions have each been ranked by 3 ZonMw staff members. The final score is based on a consensus about the individual scores.

2.6 Appraisal

For all included interventions a general appraisal of four aspects (effectiveness, cost-effectiveness, transferability, implementation) was performed using a two-star classification system. This system was developed in our former reports in the series (De Wit et al., 2007). When an aspect was given one star then the aspect was evaluated as moderate evidence/relatively unfavourable; when an aspect was given two stars then the aspect was favourably evaluated. For effectiveness, one star indicates that the body of evidence is rather moderate, while two stars indicate that there is convincing evidence on the effectiveness of the intervention. For cost-effectiveness one star indicates that the range of ICERs

(either from sensitivity analyses or from uncertainty analyses) frequently exceeds our threshold value, that the point-estimates of base-case ICERs of some studies exceeds the threshold value, or that a cost-effectiveness acceptability curve (CEAC) shows a considerable probability that the ICER will exceed the threshold value. Two stars for cost-effectiveness were given if the range of ICERs (either from sensitivity analyses or from uncertainty analyses) does not exceed the threshold, if the point-estimates of base-case ICERs did not exceed the threshold, or if no CEAC shows a considerable probability that the ICER will exceed the threshold value. For transferability one star indicates major problems with the transferability of foreign study results to the Dutch situation, and two stars indicate no major problems with the transferability, so the results of foreign studies are expected to be transferable to the Dutch situation. Finally, one star for implementation was given when the VIS-score for the majority of the criteria was less then three (on a scale ranging from 1 to 5). Two stars for implementation indicate that the majority of the criteria had a VIS-score of three or above.

3 Results

3.1 Population screening for *H. pylori* to prevent gastric disorders

3.1.1 Health problem

Helicobacter pylori (*H. pylori*) can cause a chronic infection of the gastric wall, and is associated with dyspepsia, peptic ulcer, and gastric cancer (Wijnhoven & van, 2006; Kuipers, 1997; De Vries et al., 2007a; Malaty, 2007; Makola et al., 2007). The bacterium *Helicobacter pylori* is able to survive in the acidic environment of the stomach. In the stomach, the bacterium enters the gastric mucosa resulting in an infectious reaction. This chronic infection can result in the development of gastric cancer. Gastric carcinogenesis is considered a multistep process: the chronic inflammation induced by *H. pylori* progresses slowly through premalignant stages of gastritis, metaplasia and dysplasia to gastric cancer (De Vries et al., 2007a). So, people who are infected with *H. pylori* have an increased risk of developing dyspepsia, peptic ulcer, and gastric cancer. The latter risk is increased by at least six times in *H. pylori* infected persons (De Vries et al., 2007a; Ables et al., 2007; Malaty, 2007; Lochhead & El-Omar, 2007). In 1994, the World Health Organisation (WHO) even classified *H. pylori* as a human carcinogen (IARC, 1994). In the recent 'Staat van Infectieziekten' it is estimated that, assuming an attributable fraction of 74%, over 1,000 cases of non-cardia gastric cancer were ascribed to *H. pylori* in the Netherlands in 2003 (Rahamat et al., 2007). Of all duodenal and gastric ulcers, 60-90% is associated with *H. pylori* (Festen, 2007b; van Leerdam & Tytgat, 2002). In developing countries the prevalence of *H. pylori* infection among adults is more than 80%; in developed countries this prevalence is considerably lower: 20-50% (Makola et al., 2007). In the Netherlands, the prevalence is estimated at about 20-32% (Festen, 2007b; De Vries et al., 2007b). In several ethnic groups *H. pylori* prevalence is much higher, up to 90% (personal communication, Prof. Kuipers). The incidence and prevalence of *H. pylori* infection has been decreasing for decades (Rahamat et al., 2007; Festen, 2007b; De Vries et al., 2007b; Kuipers et al., 1993; Roosendaal et al., 1997).

In the Netherlands, the incidence of gastric cancer was almost 2,000 cases (0.13 in 1,000) in the year 2003 (Poos et al., 2006a). The prevalence in that year was about 4,300 patients (0.27 in 1,000). In 2005, 1,500 patients died from gastric cancer (Poos et al., 2006a). The incidence and prevalence in men is almost twice as high as in women. In 2003, treatment of gastric cancer costed circa 52 million euros (Hoekstra & Poos, 2006). Both incidence and mortality have been decreasing during the past decades (incidence: 35% reduction since 1990, mortality: 50% reduction since 1980) (Poos et al., 2006b). The two main factors behind this decrease are: changing methods of food storage (cooling instead of pickling), and decreasing number of infections with *H. pylori* (Poos et al., 2006b). De Vries et al. found that the incidence of pre-malignant gastric lesions is also declining in the Netherlands (De Vries et al., 2007b). Based on this finding a further decline in gastric cancer incidence of circa 24% in the coming decade may be anticipated (De Vries et al., 2007b). Since early stages of gastric cancer have non-specific symptoms or no symptoms at all, gastric cancer is usually diagnosed in an advanced stage, with limited curative options. Consequently gastric cancer has a poor prognosis (five-year survival: <20%) (De Vries et al., 2007a).

Based on general practice registration networks, the year-prevalence of peptic ulcer in the Netherlands is estimated at over 40,000 patients (2.5 in 1,000), and the incidence at 8,000 cases (0.5 in 1,000) (Festen & Poos, 2007). About 10% of the population of western countries will develop a duodenal or gastric ulcer during their lifetime (Ford et al., 2006). Furthermore, many people suffer from dyspepsia

(pain or discomfort in the upper region of the abdomen). In 2001, the prevalence of dyspepsia-related complaints presented to the general practitioner was 11 in 1,000 for gastric pains, 7 in 1,000 for heartburn, and 5 in 1,000 for nausea (Linden et al., 2004). The self-reported prevalences of these dyspepsia-related illnesses were much higher (73 in 1,000, 69 in 1,000, and 61 in 1,000, respectively) (Linden et al., 2004). It should be noted that these categories are not mutually exclusive. Overall, the yearly incidence of dyspepsia in the Netherlands is estimated at 10-40% (de Wit et al., 2005). In the UK, the six-month prevalence of dyspepsia is 38% (Lane et al., 2006).

3.1.2 Current situation

Since 2004, the current practice (Dutch multidisciplinary guideline) for dyspepsia is as follows: patients presenting with dyspepsia and alarm symptoms should be referred to undergo endoscopy; patients with dyspepsia who visit the general practitioner (GP) for the first time should be given acid-suppressive drugs; only those patients with recurring dyspepsia should be tested and treated for *H. pylori*. In practice, most patients with dyspepsia receive proton pump inhibitors (PPIs): according to the second Dutch national survey of general practice, in 83% of the cases of gastric pains, and in 93% of the cases of heartburn, drugs are prescribed (mainly PPIs) (Linden et al., 2004).

3.1.3 New intervention

The intervention discussed in this chapter is population screening for *H. pylori* to prevent dyspepsia, peptic ulcer, and gastric cancer. This means that all asymptomatic individuals in a certain age group (e.g. 40-50) will be offered a screening test to detect *H. pylori* infection. Infected persons will be treated with *H. pylori* eradication therapy (a triple therapy with two antibiotics and one acid-suppressive drug).

3.1.4 Effectiveness

There are accurate, inexpensive and non-invasive tests for detecting *H. pylori* infection (e.g. breath test, serum test, stool test) (Festen, 2007a; Ables et al., 2007; Ford et al., 2006). Eradicating a *H. pylori* infection by triple therapy consisting of two antibiotics and an acid-suppressive drug is effective (70-90%) too (Ford et al., 2003). After eradication of *H. pylori*, there is only a small risk that one will be re-infected with the bacterium (Festen, 2007a). In developed countries, re-infection of adults is unusual, and recurrence usually represents failure of primary eradication rather than new infection (Parsonnet, 2003). Thus, unlike other programs, *H. pylori* screening only needs to be done once in a lifetime.

H. pylori screening and eradication has beneficial effects on dyspepsia. Trial-evidence is available for an effect on dyspepsia symptoms (Lane et al., 2006), on the number of patients consulting their GP for dyspepsia (Lane et al., 2006), and on dyspepsia-related health resource use (Ford et al., 2005; Moayyedi et al., 2000). For instance, a recent follow-up study on the effects of *H. pylori* screening (40-49 years of age) resulted in a mean saving in dyspepsia-related costs. These savings were greater than the initial costs of the screening program (Ford et al., 2005). However, none of these trials and reviews found effects on quality of life. A recent Cochrane review concluded that *H. pylori* eradication has a small benefit in initial healing of ulcers, and a significant benefit in preventing the recurrence of peptic ulcers (Ford et al., 2006). Finally, although there is a firm evidence base for the causal path from *H. pylori* infection via chronic gastritis and peptic ulcer disease to gastric cancer (Makola et al., 2007; Malaty, 2007), actual trial-based evidence of the effectiveness of population screening for *H. pylori* on gastric cancer related mortality is lacking. This might be related to the long lag time before *H. pylori* infection leads to gastric cancer (Lochhead & El-Omar, 2007; Poos et al., 2006b). Nevertheless, mass screening in Japan has resulted in increased detection of gastric cancer at an early stage. Furthermore, several uncontrolled trials have suggested that gastric cancer mortality has indeed been reduced by

mass screening (De Vries et al., 2007a; Malfertheiner et al., 2007). Moreover, several RCTs showed regression (or a decrease of progression) of precancerous gastric lesions (Malfertheiner et al., 2007). Several trials reported that eradication treatment failed tot prevent gastric cancer in people with atrophic gastritis and intestinal metaplasia (Kuipers & Sipponen, 2006). One Chinese trial reported reduced gastric cancer incidence after H pylori eradication in a subgroup without baseline atrophy (De Vries & Kuipers, 2007). This may suggest that eradication treatment to prevent gastric cancer is useful only in patients with non-atrophic gastritis (Kuipers & Sipponen, 2006). However a Japanese (nonrandomized) study showed a significantly lower incidence of gastric cancer in the eradication treatment group, including many patients with precancerous conditions like atrophic gastritis (Kuipers & Sipponen, 2006).

In the developed world, the decline in *H. pylori* infection is accompanied by an increase in gastro-oesophageal reflux disease (GERD) (Moayyedi & Talley, 2006). This observation has led to the idea that *H. pylori* might protect against GERD. Although *H. pylori* infection is indeed negatively associated with GERD, a systematic review did not any effect of *H. pylori* eradication in *causing* GERD (Moayyedi & Talley, 2006).

3.1.5 Cost-effectiveness

The literature search resulted in 6 economic evaluations of *H. pylori* screening. All studies only include direct health care costs, and conclude that onetime screening of the middle-aged population for *H. pylori* infection and consequent treatment of infected persons would be cost-effective. However, since there is no direct evidence that *H. pylori* eradication reduces gastric cancer mortality, all studies had to make assumptions about the level of this risk reduction.

Leivo et al. performed an economic evaluation of population screening of those between 15 and 45 years of age using a serum test (Leivo et al., 2004). The reference scenario was no screening and test and treat *H. pylori* only if clinical symptoms appear. It was assumed that screening and eradication would decrease the incidence of dyspepsia, peptic ulcer, and gastric cancer. The cost-effectiveness was estimated at $ 26 (2006: € 28) per screened person, and among people aged 45 years, screening was even cost saving. The incremental costs per treated *H. pylori* infection were $ 412 (2006: € 437). A thorough sensitivity analysis was carried out, resulting in relatively small changes in the ratios. The findings were most sensitive to the assumed probabilities of *H. pylori*-related lesions and cancer. The authors recognize that the pathophysiological evidence of the positive effects of eradicating *H. pylori* has to be confirmed, and that there is uncertainty on the negative effect of eradication on GERD.

Roderick et al. presented an evaluation of the cost-effectiveness of population screening in preventing peptic ulcer and gastric cancer (Roderick et al., 2003). Several age groups were modelled and it appeared that serology screening at 40-49 years of age showed the best results, balancing cost-effectiveness, absolute gains, and feasibility. Population screening between 40 and 49 years of age appeared to cost £ 5,860 (2006 €: 9,376) per LYG. The cost-effectiveness depended on the time period that was modelled: the shorter that period, the higher the ICER. Only after 20-40 years, the ICER fell below £ 20,000/LYG (2006 €: 32,000/LYG). The model assumed a time lag before eradication became effective in preventing ulcer and cancer. This made the cost-effectiveness less favourable, but it is more realistic than a fixed efficacy. There is uncertainty about the efficacy of eradication on the risk of gastric cancer, about the efficacy of eradication on the risk of complicated peptic ulcer, and about the effect of more widespread use of opportunistic screening.

Mason et al. evaluated the costs and effects of population screening on peptic ulcer and gastric cancer (Mason et al., 2002). This evaluation was based on a randomized controlled trial of screening and

treatment of *H. pylori*. The trial showed small decreases in *H. pylori* prevalence, dyspepsia scores, and dyspepsia-related costs. Nevertheless, the cost-savings were only statistically significant for men, but not for women. The cost-effectiveness model indicated that screening was the dominant strategy as it would cost less and save more lives than no screening. The two most important factors in the sensitivity analysis were: effectiveness of eradication in reducing dyspepsia costs, and effectiveness of eradication in preventing ulcer and cancer related mortality. In the worst case scenario the cost-effectiveness was less than £ 15,000 (2006 €: 24,000) per LYG. This indicated that even if the cancer mortality reduction was only 10%, the program would still be cost-effective.

In 1999, Fendrick et al. published a cost-effectiveness analysis on *H. pylori* screening of all 40 years old men (Fendrick et al., 1999). The base case analysis showed a cost-effectiveness ratio of $ 6,264 (2006 €: 7,141) per LYG. Screening plus confirmatory testing resulted in an incremental cost-effectiveness ratio of $ 37,870 (2006 €:43,172) per LYG as compared with screening without confirmatory testing. The sensitivity analyses showed that the cost-effectiveness ratio of screening without confirmatory testing varied substantially as the level of risk reduction of gastric cancer after eradication was varied. Screening remained cost-effective even at moderate (30-50%) rates of risk reduction. It should be noted that the authors used a threshold of $ 50,000 (2006 €: 57,000) per LYG.

Sonnenberg and Inadomi used a decision tree to model the costs of screening for *H. pylori* and the effects on gastric cancer mortality in the U.S. (Sonnenberg & Inadomi, 1998). They assumed the relative risk of developing gastric cancer for *H. pylori* infected persons to be four. Successful eradication resulted in a 30% risk reduction for developing gastric cancer. Their modelling exercise resulted in an ICER of $ 11,500 (2006 €: 13,110) per LYG. This result was most sensitive to assumptions with regard to prevalence of gastric cancer, costs of gastric cancer treatment, and effects of eradication.

Parsonnet et al. estimated the costs and benefits of screening for *H. pylori* at the age of 50 and treating infected individuals with antibiotics (Parsonnet et al., 1996). It was assumed that eradication prevented 30% of the attributable gastric cancers. The model resulted in an ICER of $ 25,000 (2006 €: 29,250 per LYG. This estimate was most sensitive to the effectiveness of eradication on preventing gastric cancer.

3.1.6 Transferability

The transferability of the results of the economic evaluations to the Dutch situation depends on transferability of the various assumptions in the models. The prevalences of *H. pylori* infections in the base case analyses range from 13 to 40% in the models (the sensitivity analyses use ranges from 10 to 90%). The prevalence of *H. pylori* infection in the Netherlands is estimated at 30% (De Vries et al., 2007b). The incidence of gastric cancer and peptic ulcer has been decreasing for decades, and some models were based on data of over a decade ago. So, modelling the current (lower) incidence of gastric cancer would result in a higher ICER. Finally, with regard to practice variation, all studies compared the costs and effects of screening with no screening at all, while in the Netherlands those with persisting dyspepsia are being screened (i.e. case-finding). This makes the results of the included economic evaluations not immediately transferable to the Dutch situation. Comparing population screening with the current case-finding strategy will result in higher ICERs and thus will make screening less cost-effective. Therefore, we conclude that the foreign economic evaluations are not easily transferable to the Dutch context, and that Dutch research on *H. pylori* screening is necessary.

3.1.7 Implementation

ZonMw-projects
ZonMw has not commissioned any research projects on population screening on *H. pylori*.

Relevant policy documents and guidelines
Reports about *H. pylori* infection include Management of Dyspepsia ('Maagklachten" (2000)) of the Dutch Health Council, and yearly updates of the development of *H. pylori* research provided by the European Helicobacter Study Group (chaired by a Dutch member E.J. Kuipers, ErasmusMC). The Dutch College of General Practitioners has a practice guideline for dyspepsia (2006). This guideline supports the diagnosis and treatment of *H. pylori* in the context of possible other causes, and for the whole range of gastric disorders. For patients there is an information leaflet available from their GP.

Innovation
Population screening on *H. pylori* would be a new intervention in the Netherlands. However, it is currently not under discussion, as many aspects of *H. pylori* infection are not yet sufficiently known (e.g. its relation to the development of various gastric diseases, means of transmission, and mortality reduction). In general the decision for population screening is made by the Minister of Health, Welfare, and Sport after a positive evaluation by the Dutch Health Council (Gezondheidsraad) of the various aspects of screening.

User groups
Main user groups are general practitioners, or to a lesser extent gastroenterologists. Recent knowledge about the diagnosis and treatment of *H. pylori* is available for these groups, and included in guidelines. As population screening is not to be expected soon, patients will have to be identified through case finding, according to the present guideline. It may be necessary to evaluate the extent to which general practitioners apply the guideline, particularly with respect to the diagnosis of *H. pylori*.

Resources
Population screening is funded out of the national budget, but at present population screening on *H. pylori* does not have the attention of health care policymakers. Considering the uncertainties about *H. pylori* screening, as well as the current discussion among Dutch policy makers about population screening in general (e.g. its cost-effectiveness, mortality reduction, and consequences for health care practice), it is not likely that nationwide *H. pylori* screening in the general population will be considered in the short term.

Organisation
In theory, population screening for *H. pylori* may be relatively easy to implement, because it can be carried out with a sample of blood, faeces, or breath, which adults only need to undergo once in their lifetime. It is conceivable that such a screening programme could be carried out by the general practitioner, or by a dedicated screening unit with physician assistants or nurse practitioners. *H. pylori* screening may be offered in combination with a future screening program for colorectal cancer.

Conclusion
Before policy makers can decide about implementation of population screening on *H. pylori* infection, more research is required about the mechanisms of the infection, effects of screening on diseases associated with *H. pylori*, and the efficiency and added value of a population screening compared to case finding according to the current guideline.

Dimension	**Innovation**	**User groups**	**Resources**	**Organisation**
Score*	2	2	1	2

*VIS-score; a scale for measuring implementation potential

3.1.8 Conclusion

H. pylori screening is appealing because it is a form of primary prevention, rather than secondary prevention (early detection). However, although the evidence is persuasive, it is not conclusive (Moayyedi & Hunt, 2004). For instance, evidence is lacking on the effectiveness of population screening on gastric cancer incidence and mortality, and the possible negative side-effects of eradication. The modelled effects in the economic evaluations are primarily based on the effect of eradication on gastric cancer mortality, and it is exactly this outcome that is scientifically unproven. This makes the outcomes of the cost-effectiveness analyses rather weak. Nevertheless, if a screen-and-treat strategy is effective in preventing a substantial proportion of morbidity from peptic ulcers and mortality from gastric cancer, than it will probably be cost-effective (Moayyedi, 2007). Two other problems will also have a negative effect on the effectiveness, and thus, on the cost-effectiveness of screening and treating *H. pylori*: resistence of the bacterium against the antibiotics, and compliance of the patients with the therapy. Several factors indicate that the favourable ICERs derived from foreign studies may not be directly transferable to the Dutch situation. Before policy makers can make a decision on whether or not implementing population screening on *H. pylori* infection, more research knowledge is required about the fundamental mechanisms of the infection, effects of screening on diseases associated with *H. pylori*, and the efficiency of a population screening compared to case finding according to the current guideline. Given the persistent considerable prevalence of infection in the general population, and the fact that gastric cancer remains one of the most common malignancies and has a dismal prognosis, further evaluation of research into this issue is relevant.

Table 1. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
*	*	*	*

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

3.2 Universal influenza vaccination of children

3.2.1 Health problem

Influenza is an acute respiratory illness, caused by the influenza virus. Symptoms of influenza are: fever, headache, muscle pain, sore throat, and coughing. A person with influenza generally feels weak and fatigued. The year-incidence of influenza-like illness (ILI) reported to the GP in the Netherlands has since the beginning of the century fluctuated between 10-20 (Plas, 2005). The incidence in young children is relatively high (Poos & Gommer, 2006). In the year 2006-2007, the overall incidence was 12 in 1,000, while the incidence among children 0-4 years of age was 37 in 1,000 (NIVEL CRM peilstations). These figures are based on GP registrations. Since not all people with an ILI will consult their GP, the actual incidence is expected to be much higher (Plas, 2005). Complications (like acute otitis media (AOM), pneumonia, bronchitis), and, consequently, hospitalisations, are more frequent in young children than in healthy adults (Rojo et al., 2006; Peltola et al., 2003; Neuzil et al., 2000). Hospitalisation rates in children are similar to people in high-risk groups for whom annual vaccination is recommended (Neuzil et al., 2000; Rojo et al., 2006). Furthermore, children are considered to be important transmitters of influenza in the community (via households, day-care centres, and schools) (Ramet et al., 2007; Neuzil et al., 2000; Izurieta et al., 2000; Wallinga et al., 2006).

3.2.2 Current situation in the Netherlands

Most western countries have implemented influenza vaccination programs for specific groups with an increased risk of developing severe influenza complications. In the Netherlands, the following specific high-risk groups are being vaccinated: elderly above 65 years of age (in 2008, the age threshold will be lowered to 60 years), patients with respiratory diseases, patients with chronic heart diseases, patients with diabetes, patients with chronic renal insufficiency, patients with a recent bone marrow transplantation, HIV-infected persons, children with long-term use of salicylates, institutionalized mentally handicapped persons, nursing home residents, and persons with otherwise compromised immunity (GR, 2007). In the Netherlands, general practitioners select the high-risk groups within their own patient population, and invite them for vaccination before the start of the influenza season, usually in the month of October or November. Nursing home residents who do not have a GP, are offered vaccination via their nursing home clinician.

The influenza virus changes continuously because of antigenic drift. Each year in February, based on characterisation of viruses so far, the World Health Organisation (WHO) advises on the composition of the vaccine for the next season, based on anticipated drift. If drift appears to differ from expectations, vaccine match to the circulating viruses might be suboptimal, and vaccination in one season is unlikely to provide optimal protection against the circulating virus during the next season. So, each year new vaccines have to be developed, and an influenza vaccination program therefore has to consist of annual (re)vaccinations.

3.2.3 New intervention

The intervention discussed in this chapter is influenza vaccination of all healthy children of 0.5-4 years of age. Various countries, for instance the U.S. and Canada, included vaccination of all children in their influenza vaccination scheme (AAP, 2007; ACS, 2007; Fiore et al., 2007). The American Advisory Committee on Immunization Practices (ACIP) recommended vaccination of children of 0.5-4 years of age. In the US, live attenuated vaccine is used, which is not licensed in Europe. In 2007, the Dutch Health Council advised not to extend the influenza immunization program to all healthy children, primarily because of the lack of evidence on the effectiveness of the vaccine in very young children (GR, 2007). This is in line with the recent report of the European Centre for Disease Prevention and Control (ECDC), which concluded that there are many knowledge gaps to be resolved before vaccination of all healthy children may be introduced in European countries (ECDC, 2007).

3.2.4 Effectiveness

Influenza vaccines can be distinguished into live attenuated virus vaccines, and inactivated virus vaccines. Both categories effectively and safely reduce the incidence of influenza infections in children above two years of age: the effectiveness of universal vaccination in preventing lab-confirmed influenza is 59-65% with inactivated vaccines and 72-80% with live attenuated vaccines (Jefferson, 2006; Smith et al., 2006a; Manzoli et al., 2007; Negri et al., 2005). The effectiveness against ILI is much lower (28-45% and 34-38%, respectively) because ILI is frequently caused by other viruses than influenza (Jefferson, 2006; Manzoli et al., 2007; Negri et al., 2005; Ramet et al., 2007; Smith et al., 2006b). Reviews on the effectiveness of vaccination of healthy children conclude that for children younger than 2 years of age there is insufficient (RCT-) evidence to distinguish the effects of vaccination from placebo among children under the age of two (Manzoli et al., 2007; Negri et al., 2005; Smith et al., 2006b). On the other hand, two large retrospective studies report that vaccine effectiveness among children aged 0.5 to 2 years is 49-87% (Ritzwoller et al., 2005; Allison et al., 2006). Studies in a particular season and place are difficult to extrapolate due to the annual variation in vaccine mix and

viral virulence. However, based on the latter two studies, the ACIP recently concluded that multiple studies have demonstrated vaccine efficacy among children aged ≥ 0.5 years (Fiore et al., 2007).

Vaccination could not only directly protect children against morbidity and (rarely) mortality from ILI, but it could indirectly protect the members of the households of the vaccinated children (Ramet et al., 2007). So, vaccination of children could reduce ILI related morbidity and mortality in the children themselves, and in the remainder of the population, by a decreased force of the infection in the community. The best quality study in a recent review reported significant reduction of respiratory tract infections, medical consultations, and work and school days lost (Jordan et al., 2006). Universal vaccination of children might have considerable socioeconomic benefits if absence from work of parents caring for their children is considered.

3.2.5 Cost-effectiveness

The literature search resulted in six good-quality cost-effectiveness studies on universal influenza vaccination of children. None of these was carried out in the Netherlands. Overall, the vast majority of the studies reported favourable cost-effectiveness estimates: annual vaccination of all children would save costs to society, and would be cost-effective from the health care perspective. Five studies included children aging from 0.5 to 2 years of age (Marchetti et al., 2007; Salo et al., 2006; Prosser et al., 2006; Skowronski et al., 2006). Two of these studies evaluated the costs per QALY, and reported similar ratios: € 10,000 – 13,000 per QALY, and $ 12,000 per QALY (Marchetti et al., 2007; Prosser et al., 2006).

Marchetti et al.[1] estimated the potential health and economic outcomes of a universal influenza immunization program with an inactivated vaccine in Italian children (0.5-4 years) (Marchetti et al., 2007). Assumptions on effects of vaccination on households (parents: 20% reduction of ILI, siblings: 30% reduction of ILI) were included. From the societal perspective, the immunisation program was cost-saving. From the perspective of the health care service, the cost-effectiveness of the program was € 10,000-13,000 (2006 €: 10,700-13,910) per QALY. The findings were sensitive to household protection rate, and vaccine effectiveness.

Navas et al. modelled the cost-effectiveness of universal influenza vaccination in Spanish children (3-14 years) (Navas et al., 2007). Effectiveness data were based on their own prospective cohort study. Possible preventive effects of vaccinating children on influenza incidence in non-vaccinated parents and siblings were not included, resulting in a conservative estimate. Both direct and indirect costs (productivity losses) were included. The break-even vaccine price was € 2.88 from the provider perspective and € 11.93 from the societal perspective. The program was estimated to be cost-saving from the societal perspective. The estimates were sensitive to vaccine price and costs of work absenteeism.

Salo et al. assessed the cost-effectiveness of annual influenza vaccination of all children aged 0.5-13 years (Salo et al., 2006). The immunization program resulted in cost savings in all age groups from both the societal and the provider perspective. From the latter perspective, the savings per vaccinated child were € 2.9-28.7 (2006 €: 2.78-27.55). The break-even vaccine price ranged from € 7.60 to € 11.00 (2006 €: 7.30 to 10.56). Annual influenza vaccination of all children remained cost-saving with a vaccine effectiveness of 60% (compared to 80% in the base case), and with a 50% reduction of the primary care visit rate and the emergency department visit rate.

[1] One of the authors was employed by the company that produces the influenza vaccine that was used in the study.

Prosser et al. evaluated the cost-effectiveness of annual influenza vaccination of children (0.5-17 years) (Prosser et al., 2006). They compared the use of a live, attenuated vaccine and an inactivated vaccine with no vaccination as reference scenario. Only direct medical costs were included, so a health care perspective was used. The incremental cost-effectiveness ratio increased with age: $ 12,000 (2006 €: 11,640) per QALY for children aged 0.5 -2 years, $ 18,000 (2006 €: 17,460) per QALY for children of 2 years old, and $ 28,000 (2006 €: 27,160) per QALY for children aged 3-4 years. For children over 5 years of age the cost-effectiveness was $ 79,000 to 119,000 (2006 €: 76,630 to 115,430) per QALY. The estimates were sensitive to changes in the assumed attack rate and to lesser extent to hospitalization rate, vaccine effectiveness, and total vaccination costs.

Skowronski et al. evaluated the cost-effectiveness of annual influenza vaccination of children aged 0.5-2 years with an inactivated vaccine in Canada (Skowronski et al., 2006). Including both direct and indirect costs, the analysis resulted in a cost-effectiveness ratio of CND$ 127-151 (2006 €: 96.50-114.75) per ILI averted, and CND$ 508-604 (2006 €: 386-459) per AOM averted. Costs per LYG were estimated at CND$ 864,000 (2006 €: 656,640) and CND$ 1,027,000 (2006 €: 780,520) (payers perspective and societal perspective, respectively). These estimates were sensitive to assumptions of attack rate, hospitalization rate, and costs of immunization.

Meltzer et al. evaluated the costs and effects of influenza vaccination of children (0.5-14 years) (Meltzer et al., 2005). The authors calculated the net economic returns of vaccination of several age groups. All benefits and costs were included (societal perspective). They discerned between high-risk children and low-risk children, and concluded that vaccination of the former group consistently resulted in cost savings. Vaccination of the latter group was not cost-saving and had a vaccine break even price of $ 30-60 (2006 €: 30.30-60.60) per dose. Indirect costs were the most important element of the net costs or savings. The estimates were relatively sensitive to changes in the probability of death, and to the rate of outpatient visits.

Three older economic evaluations (White et al., 1999; Cohen & Nettleman, 2000; Luce et al., 2001) of influenza vaccination of children were reviewed by Jordan et al. (Jordan et al., 2006). It was concluded that in all three studies vaccination would save costs to society. These savings were largely driven by reduced work absenteeism of the parents, although vaccination remained cost-saving in two of the studies when work absenteeism was not included.

3.2.6 Transferability

The transferability of the results of the foreign economic evaluations to the Dutch situation depend on the transferability and validity of the assumptions made in the models. This applies, for instance, to assumptions about the incidence of influenza infections and ILI during the modelled influenza seasons. The included studies assume influenza attack rates varying from 15 to 40%, with most rates around 20%. This is comparable to the Dutch rates. In most cost-effectiveness models, effectiveness was defined as the direct protective effect for the current season for those who were vaccinated. But, including the indirect effects of vaccination in unvaccinated people, and the long-term effects of a vaccination program, would imply a higher effectiveness of the program (and, consequently, more favourable ICERs). Another factor that limits the generalizability of the results is that the burden of disease for influenza is highest in very young children, while the effectiveness of vaccination is better in older children. Finally, transferability is related to possible differences in costs of the intervention. The included studies assume costs of vaccination (vaccine price plus administration costs) between €

10 and € 70. In the Netherlands the influenza vaccine costs about € 4 , and administration may cost about € 5-6, depending on the type of health care provider that is assumed to provide with the vaccine.

3.2.7 Implementation

ZonMw-projects
ZonMw has not commissioned projects on a universal influenza vaccination of children, but only of children at high risk for complications due to influenza (i.e. asthma or recurrent respiratory tract infections).

Relevant policy documents and guidelines
An advice of the Health Council of the Netherlands on *Influenza vaccination: revision of the indication* (March 2007) had been published. They advised not to include healthy children in the influenza program because of lack of evidence. However, it was recommended to perform more research into the effectiveness of vaccination for healthy children, and to reconsider the vaccination of children when new results are available. The current policy of the Dutch Minister of Health, Welfare, and Sport is according to the Health Council's advice.

Innovation
Implementing universal vaccination of children in the Netherlands would be an extension of the current policy, which only includes adults at a high risk for complications due to influenza (e.g. people with a chronic disease or aged >65 years (>60 years starting in 2008)). However, in line with the recent advice of the Health Council, it is not likely that implementation of vaccination of children will take place within the next years. In the Netherlands, influenza vaccination of healthy children must also be viewed against the background of the universal vaccination of children against pneumococcal infection, which was added to the Dutch vaccination programme in 2006. The Netherlands is the only western country which offers this vaccination in its national programme. The evidence for the effectiveness of influenza vaccinations, which is assumed in current evaluation studies, may therefore not account for the Dutch situation. Consequently, the added value of influenza vaccination for Dutch healthy children may differ from that for children in other countries.

User groups
Possible user groups for universal vaccination of healthy children are the general practitioners, the municipal health services, and the child health centres. Likely, at least a part of them is aware of the discussion about universal vaccination. However, universal vaccination is not in line with recently adopted policy. A ZonMw project showed that a serious barrier to the take-up of vaccination was parental resistance, particularly against influenza and pneumococcal infection.

Resources
Vaccination is funded out of the national budget, but at present vaccination of healthy children is not included.

Organisation
The current programme for influenza vaccination for elderly people and risk groups is very successful. It is carried out by the general practitioner, and the participation rate is good. But if universal influenza vaccination of children would be introduced, the capacity of this setting is probably not sufficient. As an alternative, children could be vaccinated by the municipal health service or at the child health centre, integrated in the existing National Vaccination Programme. But also in these settings, a yearly vaccination will lead to a substantial extra work load.

Conclusion:
Before policy makers can decide about implementation of universal vaccination of young healthy children, more knowledge is required about its effectiveness, the added value in view of vaccination against pneumococcal infection, and the acceptance of the vaccination programme by the parents.

Dimension	Innovation	User groups	Resources	Organisation
Score*	2	2	1-2	2

*VIS-score; a scale for measuring implementation potential

3.2.8 Conclusion

Although universal influenza vaccination of healthy children (e.g. 0.5 to 4 years of age) is implemented in several countries, there is no convincing evidence base for the effectiveness of vaccinating young children. A considerable amount of recent foreign economic evaluations suggest that vaccination of all children against influenza is cost-effective. So, if vaccinating all children is confirmed to be effective in preventing ILI in the children, then this strategy will probably also be cost-effective. However, if effective and cost-effective, there still are doubts about the implementation of such a strategy, given the fact that parents are rather critical towards vaccinating healthy children against an infection that is generally self-limiting and uncomplicated. More research is required on the effectiveness of vaccination in young healthy children, the added value of influenza vaccination in relation with the current vaccination against pneumococcal infection, and the acceptance of the vaccination programme by the parents.

Table 2. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
*	*	**	*

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

3.3 Universal bone densitometry screening of elderly women

3.3.1 Health problem

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (Kanis, 2002; Van der Klift et al., 2003a). Osteoporosis is assessed by measuring bone mineral density (BMD). There are four categories of BMD (Kanis, 2002):

- Normal: hip BMD greater than 1 standard deviation (SD) below the young adult female reference mean (T score ≥ -1).
- Low bone mass (osteopenia): hip BMD greater than 1 SD below the young adult female mean, but less than 2.5 SD below this value (T score < -1 and > -2.5).
- Osteoporosis: hip BMD 2.5 SD or more below the young adult female mean (T score ≤-2.5)
- Severe osteoporosis (established osteoporosis): hip BMD2.5 SD or more below the young adult mean in the presence of one of more fragility fractures.

The prevalence of osteoporosis is 52 per 1000 men and 166 per 1000 women 55 year and older (standardized to the population in 2000). Osteoporosis increases both in men and women strongly with age. The prevalence of people with osteopenia is estimated 373 per 1000 men and 490 per 1000 women of 55 year and older. The prevalence of a vertebral collapse is estimated 57 per 1000 men and 237 per 1000 women of 55 year and older. The incidence of a vertebral collapse is estimated 5.9 men per 1000 per year and 14.7 women per 1000 per year. There is a steep increase in the number of hip fractures after the 70th year (Van der Klift et al., 2003b). For women the incidence of hip fractures increases from 2 per 1000 for the age group 65-69 years aged to 28 per 1000 for those aged 85 years and older. For men in the same age group the incidence increases from 1 to 16 per 1000 (CBO, 2002). In 2001, osteoporosis was the direct cause of death among 105 persons (Van der Klift et al., 2003b). Based on the demographic development, it is expected that the prevalence of osteoporosis among women will increase with 37% between 2005 and 2025 (Blokstra et al., 2007).

Factors that unfavourably influence the composition of bone mass are: genetic predisposition, small posture, female, high age, premature menopause, low physical activity, long-term immobilization, vitamin D deficiency, low dietary calcium intake, cigarette smoking, excessive alcohol consumption, particular hormonal diseases and other diseases which influence calcium- and bone metabolism (Van der Klift et al., 2004; Kanis, 2002). Risk factors that can be used for detecting people with a high risk of fractures are (Van der Klift et al., 2004):

- Previous fracture at the age of 50 years and older
- Existing vertebral fracture
- Fractures within the family, especially hip fracture of the mother
- Low bodyweight
- Serious immobility
- Use of corticosteroids

The quality of life decreases with the total number of fractures. Women with vertebral fractures had less energy and a lower quality of life than women without fractures, especially with regard to physical mobility, sleeping, social activities and emotional functioning (Wolleswinkel-van den Bosch et al., 2002).

The costs of cure and care of osteoporosis in the Netherlands in 2003 were estimated € 500 million, of which almost 100 million were no-fracture costs (for example medicines). The other € 400 million are only the direct medical costs from the hospital, nursing home and ambulant clinical care sectors (Slobbe et al., 2006).

3.3.2 Current situation

The Dutch CBO guideline osteoporosis and the Dutch general practitioners guideline recommend BMD measurement only in the following situations (CBO, 2002; NHG, 2005):

- Women aged 50 years and older with one of more fractures after the age of 50 years
- Women of 60 years and older with three of the following risk factors and women of 70 years and older with two of the following risk factors: positive family anamnesis, low body weight and serious immobility
- Women with a vertebral fracture, independent of age

Those diagnosed with osteoporosis (T<-2,5) are prescribed alendronate or risedronate[2] according to the Dutch guideline (CBO, 2002; NHG, 2005).

Based on the 1996 meta-analysis of Marshall et al. (Marshall et al., 1996), the CBO guideline recommends the measurement of BMD only as part of case-finding and not for screening of the general population. The single use of the BMD measurement in determining the risk of an osteoporotic fracture has a low sensitivity (about 50%). This means that half of all osteoporosis related fractures take place in the group which falls outside the BMD-criterion of osteoporosis (T-score < -2.5) as formulated by the WHO.

3.3.3 New intervention

Universal bone densitometry screening among women aged 70 years and older, and subsequent treatment if found eligible.

3.3.4 Effectiveness

Although many studies have been published about osteoporosis in postmenopausal women, no trials have evaluated the effectiveness of screening. There are no randomized trials comparing densitometry with doing nothing (Nelson et al., 2002; Cummings et al., 2002). Hence the evidence level for effectiveness of screening is relatively poor as it is not based on meta-analyses and RCTs, but on observational studies. Schott et al. constructed, based on an epidemiological multicentre prospective cohort study, a receiver operating characteristic (ROC) curve for BMD measurement of the femoral neck predicting hip fractures in elderly women (75 years and older) living at home (Schott et al., 1998). The area under the ROC curve for femoral neck BMD is 0.70 (95% CI: 0.69-0.71), indicating the average sensitivity over all possible specificities (Seltzer et al., 1998). Schott et al. reported that the average sensitivity of dual-energy X-ray absorptiometry (DEXA) screening in all women aged 70 years to predict hip fracture is 0.76 and the average specificity is 0.58 (Schott et al., 2007). The sensitivity is 0.75 and the specificity is 0.54 if only women with at least one risk factor should been screened. In a review of Nelson et al., including 18 studies of risk factor assessment, concluded that support for population screening would be based on evidence that the prevalence for osteoporosis and fractures increase with age, that the short term risk for fracture can be estimated by bone density tests and risk factors and that fracture risk among women with low bone density can be reduced with treatment (Nelson et al., 2002). Age-based screening is supported by prevalence data, that is, the number needed to screen (NNS) to prevent fractures decreases sharply as age and prevalence increase. The NNS to prevent 1 hip fracture is for the age 60-64 years: 1856, for the age 65-69 year: 731 and for the age 70-74: 254. The corresponding NNS to prevent 1 vertebral fracture is 458, 248 and 105 respectively.

3.3.5 Cost-effectiveness

Four economic evaluations of screening and treatment of postmenopausal women were found in the literature. Two of them were carried out in the USA, one in France and one in Switzerland. All studies were of good quality.

Mobley et al. concluded that screening and treatment with alendronate is more cost effective than screening and treatment with raloxifene[3] or hormone replacement therapy (HRT)[4]. They assumed that

[2] Alendronate and risedronate are bisphosphonates which act as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

[3] Raloxifene is in a class of medications called selective estrogen receptor modulators (SERMs). It works by acting similar to oestrogen, a female hormone produced by the body. Like estrogen, raloxifene increases the density of bone.

women were screened with DEXA at age 65 years. Relative to a no-screen, and no-therapy strategy, alendronate had an ICER (costs per QALY) of $72,877 (2006 €: 69,233). The authors reported that only hip and vertebral fractures were modelled, thus the potential benefits derived from the reduction of other fractures were not considered (Mobley et al., 2006).

Schousboe et al. (Schousboe et al., 2005) compared bone densitometry of the hip, with 5 years of alendronate therapy for subjects with osteoporosis versus no intervention. The ICER (cost per QALY) was $40,000 (2006 €: 40,000) for 65-year old women and $5,600 (2006 €: 5,600) for 75-year old women. For 85- and 95-year old women the screen and treatment strategy was cost saving, meaning less costs and more effects. The included costs were: costs of screening (including bone densitometry, a physician visit and nursing time for women living in a nursing home), alendronate, treatment of fractures and long-term care after hip fracture.

Schott et al. compared two screening strategies with no screening. The two strategies were screening women at risk and screening all women aged 70 years and older. The model incorporated costs of BMD testing (one per woman), costs of preventive treatment for women with a low BMD (based on risedronate and alendronate), cost of hospitalization and rehabilitation of patients with a hip fracture, cost of institutionalization and the costs of a screening campaign. The model was based on BMD testing of the femoral neck and on only one measure within ten years of follow up. The ICER of screening women at risk versus no screening was €8,290 (2006 € 8,539). The ICER of screening all women versus no screening was lower, namely €4,235 (2006 €: 4,362) (Schott et al., 2007) .

Schwenkglenks and Lippuner published the results of research with European input data in their model, including the results of the Rotterdam Study (Schuit et al., 2004). The ICER (costs per QALY) of a population based screening and treatment strategy among women aged 65 years at model entry, was CHF 55,533 (2006 €: 29,432) versus no screening. The ICER of a population based screening and treatment strategy women aged 75 years at model entry, was CHF 11,904 (2006 €: 6,309) (Schwenkglenks & Lippuner, 2007).

3.3.6 Transferability of foreign study results to Dutch context

Within Europe, the prevalence of osteoporosis is highest in Scandinavian countries and lowest in Eastern-Europe. The prevalence in the Mediterranean and in Western-Europe is almost the same and lies between the high Scandinavian and relatively low Eastern-European levels. The prevalence in the U.S. is a little below the prevalence in the Netherlands (van der Wilk et al., 2003). As all studies described above were performed in countries with lower osteoporosis prevalence than in the Netherlands, this contributes favourably to the transferability of foreign study results to the Dutch context. The economic evaluation of Schwenkglenks and Lippuner used European effect data, including results of the Rotterdam Study (Schwenkglenks & Lippuner, 2007) . There is no big differences with the cost level of screening as used in the US economic evaluations (Mobley et al., 2006; Schousboe et al., 2005). All authors used a discount rate of 3% for both costs and effects, with the exception of Schottt et al., they used a discount rate of 5% for costs and 0% for effects (Schott et al., 2007). Taking into account that the Dutch recommendations for discounting are 1.5% for effects and 4% for costs (CVZ, 2006), the ICERs translated to a Dutch situation are probably more favourable (with exception of Schott et al. 2007).

3.3.7 Implementation

ZonMw projects

[4] Because of the well-known disadvantageous impact of use of oestrogens in the period round and after the menopauze and the availability of sufficient alternatives there is no more place for oestrogens at the prevention of postmenopauzale osteoporosis

There is one ongoing ZonMw project on the implementation of screening for osteoporosis, and treatment of high-risk fracture patients by an osteoporosis nurse practitioner.
The results of this study - expected in March 2010 - will determine the effect in routine practice of an osteoporosis nurse in the screening on and treatment for osteoporosis in elderly patients presenting with a fracture. This study teaches us that the current guidelines on osteoporosis screening and treatment for osteoporosis are often ignored. Patients are often unresponsive to screening on osteoporosis and are non-compliant to their treatment (use of prescribed medicines). This impression is confirmed in a recent advice of the Dutch Health Council on screening for osteoporosis in the general practice (October 2007).

Relevant policy documents and guidelines
In our advice we incorporate the recommendations in:

- The multi-disciplinary CBO guideline *Osteoporosis* (2002)
- The practice guidelines *Osteoporosis* of the Dutch College of General Practitioners (2005)
- The advice of the Dutch Health Council on *Screening for osteoporosis in the general practice* (2007)

The guidelines only advise screening for osteoporosis for high-risk groups. For screening for osteoporosis the bone mineral density (BMD) of the patient is measured. This can be performed by various specialists, such as the orthopedist, the rheumatologist, et cetera., with a referral from the general practitioner. Screening for osteoporosis is expensive and has a low sensitivity for the general population. According to the guidelines and the advice of the Dutch Health Council, it is therefore only indicated for high risk groups. For these groups it is likely that treatment for osteoporosis is necessary and effective in preventing osteoporotic fractures.

Innovation
Screening of all women aged 70 years and older would imply an extension to the current practice, since age and gender are not mentioned in the current guidelines as independent risk factors for getting an osteoporotic fracture. Compared to current practice, the added value of BMD measurement in all women aged 70 years and older can be doubted. The sensitivity and specificity of the BDM measurement is slightly higher in this specific group, but still low. Moreover, the cost-effectiveness of this screening strategy has not been proven in the Dutch context.

User Groups
If screening of all women aged 70 years and above would be implemented, the follow up of procedures by the specialists, the adherence of patients to osteoporosis screening and the non-compliance of patients to the treatment for osteoporosis, would be a matter of extra attention.

Resources
Resources are available for screening and prescribed medicines. In case of population screening for osteoporosis, resources for screening would be made available from the national budget. In case of an extended case finding practice on osteoporosis, resources would be made available from health insurers. In both cases, medicines are paid by health insurers. The question is whether or not under the given circumstances decision makers are willing to make extra costs on screening for and treatment for osteoporosis.

Organisation

The follow up of the current guidelines is problematic. Similar problems can be expected if the current screening practice for osteoporosis would be extended.

Conclusion
For an implementation action, the screening for osteoporosis has to be in line with the traditional criteria of Wilson and Jungner. Currently this is not the case. The BMD measurement therefore is only advised for case finding in high risk groups and not as an instrument for screening in a 'general population'.

Dimension	Innovation	User groups	Resources	Organisation
Score*	2	2	5	1

*VIS-score; a scale for measuring implementation potential

3.3.8 Conclusion

Based on the demographic development, an increase of 37% is expected in the absolute number of women with osteoporosis between 2005 and 2025. In 2003 the costs of cure and care of osteoporosis in the Netherlands were estimated at € 500 million. The Dutch CBO guideline concluded that the sensitivity of screening all post menopausal women is too low (45%). Recently, the Dutch Health Council confirmed this guideline and brought out a negative advice to the Minister of Health concerning a permission request of the Stichting Osteoporose Casefinding Nederland (Foundation Osteoporosis Case-finding Netherlands) to screen in practices of general practitioners (Gezondheidsraad, 2007). The intervention described in our report concerns screening of all women aged 70 years and older. In this age group, the sensitivity changes from 45% to 70%. It is worthwhile to investigate whether there is enough support to implement this screening.

Table 3. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
*	*	**	*

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

3.4 Low-dose aspirin to prevent cardiovascular disease

3.4.1 Health problem

Cardiovascular Diseases (CVD) are the leading cause of death in the Netherlands. In 2006, 32% of the total mortality was due to CVD, resulting in about 43.000 deaths due to CVD. The greatest part of mortality within CVD is caused by coronary heart disease (CHD) (29%) and cerebro vascular accidents (CVA) (23%). Within the category CHD, acute myocardial infarction (MI) has the greatest contribution (70%) (Vaartjes et al., 2007). Several modifiable risk factors for CVD are known: lifestyle, e.g. smoking, dietary habits and physical inactivity and physiological risk factors such as blood pressure, serum cholesterol and obesity. Lifestyle factors are partly related to the physiological factors.

3.4.2 Current situation

Aspirin, or acetylsalicylic acid is often used for its analgesic, antipyretic and anti-inflammatory effects. In addition, aspirin also has an antiplatelet ('blood-thinning') effect. The Dutch multidisciplinary CBO guideline 'Cardiovasculair Risicomanagement' (Cardiovascular Risk management) (CBO, 2006) describes that there is not enough evidence for a standard treatment with aspirin for people without CHD. The recommended policy for persons with a high risk of CVD, but a low (10-years risk < 5%) risk of death is a lifestyle advice including smoking cessation, reduction of excessive alcohol use, healthy nutritional behaviour (less saturated fatty acids and salt, 200 gram vegetables, 2 pieces of fruit and 1 or 2 times fatty fish a week), and sufficient physical activity (at least 30 minutes physical exercise during 5 days a week).

3.4.3 New intervention

The intervention consists of a low dose of aspirin (75-150 mg.) to prevent CVD among individuals whose 10-years risk of a first coronary event is 10% or greater [the absolute risk of a fatal CVD risk ≥ 5% over 10 years (SCORE) corresponds to the formerly used 20% absolute risk of a composite of CHD events (Framingham)].

3.4.4 Effectiveness

One of the conclusions of a collaborative meta-analysis of 287 randomised trials of antiplatelet therapy in 2002 performed by the Antithrombotic Trialists' Collaboration (ATC, 2002) was that low dose aspirin (75-150 mg. daily) is an effective antiplatelet regimen for long term use for the primary prevention of death, MI and stroke. Non-fatal MI was reduced by one third. Aspirin was protective in most types of patients at high risk of occlusive vascular events.

In the Dutch multidisciplinary guideline it is explained why the use of antiplatelet prophylaxes by persons without CVD is not recommended. This is based on two meta-analyses, Sanmuganathan et al. and Hayden et al.. In this meta-analyses, it is argued that the risk on gastro-intestinal bleeding and hemorrhagic stroke is too high and that the disadvantages outweigh the advantages (Sanmuganathan et al., 2001) Sanmuganathan et al. described that aspirin treatment for primary prevention is safe and worthwhile at coronary event risk ≥ 1.5% year. The conclusion of Hayden et al. was that the net effect of aspirin improves with increasing risk for CHD. Aspirin for primary prevention significantly reduced all cardiovascular events by 15% (95% CI 6-22) and reduced MI by 30% (95% CI 21-38). The article of Hayden was a summary of the evidence for the U.S. Preventive Services Task Force (USPSTF). Aspirin reduced the risk for the combined end point of nonfatal MI and fatal CHD (pooled odds ratio 0.72, 95% CI 0.60-0.87). For 1000 patients with a 5% risk for CHD events over 5 years, aspirin would prevent 14 MI (range 6-20), but would also cause 1 hemorrhagic stroke (range 0-2) and 3 major gastro-intestinal bleeding events (range 2-4). The USPSTF concluded that the balance of benefits and harms is most favourable in patients at high risk for CHD (those with a 5-years risk ≥ 3%) but prescription is also influenced by patient preferences (USPSTF, 2002). The American Heart Association guidelines for primary prevention of cardiovascular disease and stroke recommend low-dose aspirin in persons at higher CHD risk (especially those with 10-years risk of CHD ≥ 10%) (Pearson et al., 2002). They advise not to use aspirin in persons at increased risk for gastro-intestinal bleedings and hemorrhagic stroke. The systematic review of Eidelman et al. concluded that the current totality of evidence provides strong support for the initial findings from the Physicians' Health study (SCPHSRG, 1989) that aspirin reduces the risk of first MI. Aspirin was associated with a significant 32% reduction of the risk of a first MI and a significant 15% reduction in the risk of all important vascular events. So, according to the USPSTF and the American Heart Association, the benefits of long-term aspirin therapy are likely to outweigh these risks for apparently healthy individuals whose 10-years risk of a

first coronary event is 10% or greater (Eidelman et al., 2003).The meta-analysis of six trials about the use of aspirin from Bartolucci and Howard supports the current recommendations for aspirin use when the benefits of a CVD risk decrease outweigh treatment risks in most patients at higher coronary risk (10-years risk of CHD ≥ 6%) Among subjects treated with aspirin there was a significantly ($p<0.001$) decreased risk of total CHD, nonfatal MI and total CVD events (Bartolucci & Howard, 2006). Finally, the sex-specific meta-analysis of Berger et al. reported that the favourable effect of aspirin on the combined risk of cardiovascular events for women and men is apparent from the randomized studies (included in the meta-analysis). However, they found that aspirin use is also associated with a significant risk of major bleeding irrespective of sex. Both the beneficial and harmful effects of aspirin should be considered by the physician and patient before initiating aspirin for the primary prevention of cardiovascular disease in both sexes (Berger et al., 2006).

3.4.5 Cost-effectiveness

The literature search resulted in five economic evaluations of the use of low-dose aspirin in the primary prevention of cardiovascular disease (CVD). Three of these studies included only men and two studies included both sexes. The five studies were of good quality and are described in this section.

One of the studies, by Franco et al., was performed in the Netherlands. This study included only men. The conclusion of this study was, that for cost effective pharmacological prevention of coronary heart disease (CHD), the first line of intervention should be smoking cessation therapy for smokers and aspirin at all levels of risk. Compared with smoking cessation (one of the measures according to the Dutch multidisciplinary CBO guideline), aspirin is cost-effective for moderate risk populations aged 60 years (ICER € 15,799 LYS; 2006 €: 16,431) and for high-risk populations irrespective of age (50-years: ICER € 9,336 LYS=2006 € 9,709 and 60-years: ICER € 7,213=2006 € 7,502). At population level, antihypertensive drugs (that are recommended in the Dutch CBO guideline) are dominated by aspirin treatment (Franco et al., 2007).

Lamotte et al[5] and Annemans et al.[6] published both an economic evaluation about research performed in four European countries: UK, Germany, Spain and Italy. The publications included both men and women. The first of these two publications (Lamotte et al., 2006a) concluded that, with an annual risk on CHD of 1,5% or higher and maximal risk for stroke and gastrointestinal bleedings, aspirin is dominant compared with doing nothing. The conclusion of the second publication (Annemans et al., 2006) is that for UK, Germany and Spain, aspirin is dominant compared with no therapy at a 10 years risk of fatal CVD of 2%. In Italy the risk cut-off point is higher (3%) because of the higher cost of gastrointestinal bleeding.

The research of Pignone et al. in men only showed that compared with no treatment, aspirin is less costly and more effective for preventing CHD events in middle-aged men whose 10-years risk for CHD is 7.5% or higher. In this case, the probabilistic sensitivity analysis (PSA) demonstrated with a 91% probability that aspirin is more effective and less expensive than no treatment. In the case of a 10-years risk for CHD of 10% the PSA showed a 95% probability that aspirin is more effective and less costly (Pignone et al., 2006)[7].

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[5] The study was sponsored by an unrestricted grant from Bayer HealthCare AG Germany. Thomas Evers contributed to the literature search and report writing, and is a Bayer AG employee. Maria Kubin contributed to the report review, is a Bayer AG employee and owns some employee stocks.

[6] This study was carried out by Health Economics and Disease Management, IMS Unit, under an unrestricted grant from Bayer Healthcare AG, Wuppertal, Germany.M.Kubin and T. Evers are both employees of Bayer AG. Conflicts of interest: none.

[7] **Grant support**: By Bayer (Dr. Pigne) and by grant number 1P30CD000138-01 from the Centers for Disease Control and Prevention (Dr. Pigone). **Potential Financial Conflicts off Interest**: *Consultancies:* M. Pigone (Bayer, Pfizer Inc.); *Honoraria:*

Pignone et al. also published the results of a study performed by 65 years-old women with a 7.5% 10-year risk of CHD and a 2.8% risk of stroke. Aspirin use cost $13,300 (2006€: 12,103) per additional QALY. PSA showed a 27% chance that aspirin produces fewer QALYs than no treatment.. The probability that the cost-utility ratio was greater than $ 50,000 (2006€: 45,500) was 37% (Pignone et al., 2007).

The Japanese study of Tsutani et al. including men and women demonstrated for patients with a 1-year risk of CHD of 1.5% or above, dominance of aspirin treatment compared with no treatment (Tsutani et al., 2007)[8].

3.4.6 Transferability

No major problems are expected with the transferability of the outcomes of the economic evaluations to the Dutch situation.The incidence of CVD in the Netherlands does not show a great difference with other West-European countries (van der Wilk et al., 2006b). The economic evaluations included a Dutch study and a study which was done in more countries, among which Germany. There are no differences between the prices for aspirin (100mg) between the countries. The discount rates used in the economic evaluations are 3% and more, depending on local recommendations in different countries, for both costs and effects. The discount rates in the Netherlands are 4% for costs and 1.5% for effects. Taking this into account the cost-effectiveness ratios will probably be more favourable in the Dutch context.

3.4.7 Implementation

ZonMw projects

ZonMw commissioned three projects on this subject. Two research projects (model simulation studies) showed positive results on prescription of aspirin for subjects with a CVD risk higher than 10-15%. At present, a simulation study is running to evaluate the benefits (prevented strokes and other ischemic events) and the risks (haemorrhage) of using aspirin for several target groups. Preliminary results suggest that it could be cost-effective to prescribe aspirin for males aged 55 years and older with a CVD risk higher than 10%. There is not yet enough evidence to determine which other subgroups would benefit.

Relevant policy documents and guidelines

The assessment of the implementation aspects are also based on Dutch guidelines and an expert meeting:

- Dutch guideline Cardiovascular Risk management by the Dutch Institute for Healthcare Improvement (CBO).
- Guidelines by the Dutch College of General Practitioners (NHG) on Cardiovascular risk management (2006).
- Position statement of the Netherlands Heart Foundation.
- Expert meeting priority medicines and cardiovascular diseases (ZonMw, 27 June 2007).

Innovation

Aspirin is prescribed for all patients with a CVD (except some subgroups) according to the guidelines (CBO, NHG). The Netherlands Heart Foundation stated that aspirin may be prescribed for people with

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M. Pigone (Bayer, Pfizer Inc.); *Expert testimony:* M. Pigone (Bayer); *Grants received:* M. Pigone (Bayer), S. Earnshaw (Bayer); *Other:* M. Pigone (Bayer).

[8] Atura Igarashi: Product Development Division Bayer Yakuhin Ltd., Osaka. Thomas Evers and Maria Kubin: Product Development Division, Bayer Health Care, Wuppertal.

certain risk factors such as high blood pressure as well. However, also for these people aspirin may include a risk of harmful effects (e.g., haemorrhage). Therefore, the physician must consider the benefits and risks of aspirin together with the person before starting a preventive treatment.

User groups
The main user groups are general practitioners (GP) and cardiologists, and to a lesser extent other specialists (e.g., neurologists and vascular physicians). According to the guidelines patients with CVD are offered non-drug therapies (life-style programmes) together with drugs. Although GP's are used to prescribing aspirin for other symptoms (it is within the top 10 of most prescribed drugs for GP's), GP's and cardiologist are careful in prescribing aspirin for people with (a high risk for) CVD. The main reason for this is the possibility of harmful effects of aspirin. Experts notice that the overall compliance of physicians to offer a complete therapy to heart patients, including aspirin, is low. As the recommendation of the Netherlands Heart Foundation is not part of the CBO/NHG guidelines, prescription of aspirin for a larger multifaceted risk group may therefore be even more difficult to comply to.

Resources
Aspirin is an inexpensive self-care medication, which is available over the counter. However, for people with (a high risk for) CVD aspirin must always be prescribed by a physician. As health insurers only reimburse drugs which are recommended by guidelines, aspirin is reimbursed only for patients with a CVD, and not for high risk groups.

Organization
User groups have discussed the available knowledge for the recent guidelines.

Conclusion
Although research shows beneficial effects of aspirin for patients and high risk groups, for some people with (a high risk for) CVD these positive effects do not outweigh the disadvantages. Therefore, more research is needed for recommendations on prescribing the dose of aspirin for people with different levels of risk for CVD levels of risk for CVD. At present, the barrier for implementation may be that physicians are reluctant to prescribe aspirin, because they are concerned about side effects, and alternative treatments (other drugs and lifestyle programmes) are available.

Dimension	Innovation	User groups	Resources	Organization
Score*	3	2	2	2

- Vis-score: a scale for measuring implementation potential

3.4.8 Conclusion

CHD is the leading cause of death in the Netherlands. Research shows that in individuals at high risk for CVD (10-year risk ≥10%), aspirin is a cost-effective intervention to lower the risk. However, due to the side effects (gastro-intestinal bleeding, haemorrhagic stroke) aspirin is not suitable for all individuals. Recent economic evaluations show the cost-effectiveness of the use of aspirin in the risk group, taking into account these risk factors. On the one hand the Dutch CBO guideline indicates that the advantages do not outweigh the negative effects, on the other hand the European guideline recommends the use low dose aspirin in the mentioned risk group (De Backer et al., 2003). Based on the results showed in the economic evaluations, it seems to be a good option to prescribe individuals with a 10-years risk of a first cardiovascular event of 10% and higher low dose aspirin in the prevention of cardiovascular disease.

Table 4. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
**	**	**	*

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

3.5 Exercise programme to prevent falls in elderly

3.5.1 Description of the health problem

One in three independently living elderly falls at least one time a year. Almost 70% of in the community dwelling elderly people experiences physical consequences from a fall, 6% has a serious injury like a fracture, and almost a quarter (23.5%) makes use of health care (general practitioner, physical therapist, admission in a hospital or nursing home) after a fall. Almost one third of the elderly reports a decrease in functioning after the last fall, 17% is socially less active, and 15% is physically less active. Ultimately, a fall can lead to loss of independency (CBO, 2004).

3.5.2 Current situation

The CBO multidisciplinary guideline 'Preventie van valincidenten bij ouderen' ('Prevention of fall incidents in elderly') (CBO, 2004) gives the recommendation that an exercise program is extremely worthwhile for elderly with a history of falling. According to this guideline, prevention of fall related fractures should concentrate on elderly with osteoporosis or a documented low bone mineral density.

3.5.3 New intervention

The intervention described in this paragraph is a program consisting of two components: muscle strengthening and balance training. The target group is independently living elderly. The intervention is performed individually at home by a trained health professional.

3.5.4 Effectiveness

In a meta-analysis on preventing falls in older people, Robertson et al. concluded that there is sufficient evidence to support widespread implementation of the home exercise program (provided by physiotherapists or nurses) to prevent falls. The number of falls was 35% less in the intervention group than in the control group (pooled Incidence Rate Ratio 0.65, 95% CI = 0.57-0.75) (Robertson et al., 2002). In a 2003 Cochrane review (Gillespie et al., 2003) about interventions to prevent falls in elderly people, the authors' conclusions was that interventions are likely to be beneficial. The intervention significantly reduced the number of individuals sustaining a fall over an one year period (pooled RR 0.80, 95% CI .066-0.98). The research of Luukinen et al. on pragmatic exercise-orientated prevention of falls among the elderly, confirms the findings of Robertson et al., that a programme, implemented by community nurses under surveillance by physiotherapists in primary health care practice, can reduce fall risk (Robertson et al., 2001b) . The Luukinen study also confirms the findings of Gardner et al., that the intervention improves balance among older adults, who are cognitively unimpaired, able to move around their residence (Gardner et al., 2002). After the intervention period, impaired balance was less common in the intervention than in the control subjects; 45% and 59% respectively ($p<0.05$). They recommended the implementation of home-based exercise interventions to delay the impairment of balance among the most elderly home-dwelling subjects and to prevent falling among those able to move outdoors. Compliance with the suggested interventions should be paid special attention to.

3.5.5 Cost-effectiveness

There are four studies that evaluated the cost-effectiveness or a benefit to cost ratio (BCR) of an exercise program to prevent falls among independently living older people. All studies were of good quality.

Beard et al. calculated the BCR of 'Stay on Your Feet' (SOYF), a community-based falls prevention program targeting at all people aged over 60 years and living independently (SOYF was undertaken in the North Coast region of New South Wales, Australia). They presented the results as a net present value (NPV, where NPV = benefits minus cost) and a BCR. The NPV from the healthcare perspective was Aus$ 9,989,834 (2006 €: 8,591,257) with a BCR of 13.75:1. From the societal perspective, including healthcare savings and intangible savings, program costs and community costs, the NPV was Aus$ 15,766,210 (2006 €: 13,558,940) and a BCR of 20.6:1 (Beard et al., 2006).

Robertson et al. performed in a controlled trial a study on the effectiveness and the cost-effectiveness of a home based, individually tailored, muscle strengthening and balance training programme, designed to prevent falls in elderly people living in the community. The participants were men and women aged 80 years and older. The ICER per fall prevented was NZ$ 1,519 (2006 €: 1,200). The ICER per injurious fall prevented was NZ$ 3,404 (2006 €: 2,689) (Robertson et al., 2001b). From the same authors, another economic evaluation was published of a randomized controlled trial with two years follow up (Robertson et al., 2001a). The study included women aged 80 years and older, who were living in the community. The ICER per fall prevented was NZ$ 314 (2006 €: 248) after one year and NZ$ 265 (2006 €: 209) after two years. The ICER per fall resulting in a moderate or serious injury prevented was NZ$ 457 (2006 €: 361) after one year and NZ$ 426 (2006 €: 337) after two years. Cost effectiveness ratios were lower after two years than after one year, because there are no program development costs and no materials costs in the second year, and appeared robust to changes in the cost scenarios. The differences in the ICERs in the two studies from New Zealand are caused by the different average costs per participant: NZ$ 418 (2006 €: 330) (Robertson et al., 2001b) versus NZ$ 173 (2006 €: 137) (Robertson et al., 2001a).

Rizzo (USA) et al.described an intervention including a combination of behavioural changes (e.g. improved sleep habits), medication adjustments, environmental modifications and exercises. The exercise component included progressive balance training and muscle strengthening exercises using elastic bands. Men and women aged 69 years and older, who were living independently, were included in the randomized controlled trial. The ICER per fall prevented and per medical fall prevented were both below zero, which means that the intervention was associated with both reduced health-care costs and less falls (Rizzo et al., 1996).

3.5.6 Transferability

The incidence rates used in the economic evaluations correspond with the Dutch rates as mentioned in the CBO guideline. The honorarium of a physical therapist used in the economic evaluations is comparable with the contemporary honorarium of a Dutch physical therapist (early 90th €12 and nowadays €28 per session). Only in the study of Beard et al.(Beard et al., 2006) a discount rate of 8% was used for both costs and effects. In the Netherlands a discount rate of 4% is used for costs an 1.5% for effects. Taking this into account, it is likely that the intervention will be cost-effective in the Dutch context as well.

3.5.7 Implementation

ZonMw projects
Several ZonMw-projects are aiming at a population at risk of falling. In these projects, fall prevention interventions have not been very successful in reducing fall related injuries. Although a couple of fall prevention strategies have been tested in local communities, the intervention period has been too short to see a reduction in fall accidents. If effects of interventions are observed, they are often limited to a rise in awareness (in the community, politically or personally) of the risks of falling. Sometimes interventions are also effective in reducing the fear of falling and stimulating people not to avoid certain activities. These effects seldom maintain over the long term. Examples of these 'limited-effects'-interventions are *Halt! U Valt, Beter in Balans en Vallen Verleden Tijd*.

Relevant policy documents and guidelines
The Dutch Institute for Healthcare Improvement (CBO) multidisciplinary guideline 'Preventie van valincidenten bij ouderen' recommends a fall prevention programme for people who are at risk of falling. Relevant risk factors are among others: a history of falling, an age over 65 years and physical inactivity. The risks of getting a fracture as a consequence of falling are higher for people with osteoporosis or a documented low bone mineral density. A physical training and balance programme for people over 65 years could therefore be relevant, although an intervention programme targeted at people with a combined higher risk of falling and a higher fracture risk might be more cost-effective.

Innovation
A cost-effective strategy in reducing fall related injuries implemented in the local community would be new. But it seems hard to structurally put fall prevention, especially in relation to the decrease in mobility, the most important determinant of falling, on the agenda of politicians (national and local), prevention workers and people who are at risk of falling. Campaigns and preventive interventions so far have not been capable of changing that.

User groups
High risk groups are known. But the people who are at risk are often not sufficiently aware of their risk. They are not naturally interested to participate in a fall prevention programme. They experience no problem, even if they fall once or twice a year. So there seems to be no need for a solution, not incidently and certainly not structurally.

In general the level of participation and compliance of elderly people in physical training programmes (not primarily aiming at the prevention of fall related injuries) is poor and changing over time. Some training programmes –GALM, Meer Bewegen Voor Ouderen – are successful in acquiring participants, although it remains difficult to include those who are the most vulnerable in terms of health. Once people are participating, it is hard to motivate them to be compliant to their improved level of physical activity during as well as after the intervention period.

A couple of local communities are active in executing a fall prevention intervention, and several organisations are experienced in organising such an intervention. Of this we have learned that the implementation of an intervention programme on the community level can only be successful if the political conditions in the community are supportive and if the intervention programme is structurally embedded. In the Netherlands, a Knowledge Centre for Fall Prevention actively offers scientific and practical knowledge relevant for fall prevention. It is important to develop programmes for different target groups, taking into account the relation between load and carriability.

Resources
In the local community, municipal resources (WCPV, WMO) for prevention are available but limited. Fall prevention is just one of the subjects to possibly spend money on. A high ranking of fall prevention on the list of local priorities is not self-evident.

Organisation
Some organisations are able to successfully execute a fall prevention intervention in the local community. But proven cost-effective interventions and structural funding in the Dutch context, are lacking.

Conclusion
Till now, the community experiments with fall prevention interventions lack a promise for continuity. Even if fall prevention is considered as a local priority, it seems difficult to hold on to this priority long enough to reach significant health effects. Fall prevention should rather be part of a broader 'quality of life policy', in connection with environmental and social conditions.

Dimension	Innovation	User Groups	Resources	Organisation
VIS-score[1]	2	2	2	2

[1] VIS-score: a scale for measuring implementation potential

3.5.8 Conclusion

One in three independent living elderly falls at least one time a year. The international literature shows the effectiveness of fall programmes for independent living elderly. The economic evaluations described, show the cost-effectiveness of fall-prevention programmes. ZonMw describes that the community experiments with fall prevention interventions lack a promise for continuity. Further research is necessary to investigate why the compliance is low and how this problem can be solved. It is also necessary to investigate, how to imbed fall prevention into other policy targets, like promoting the ability to do things independently and decreasing the burden of disease.

Table 5. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
**	**	**	*

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

3.6 PUFAs as tertiary prevention[9] after myocardial infarction

3.6.1 Health problem

In 2006, almost 325,000 patients were hospitalized for coronary vascular disease (CVD). Of these hospitalizations 27% (87.000) were due to ischemic coronary heart disease (CHD), of which 24,000 were myocardial infarctions (MI) (Vaartjes et al., 2007). Taking into account the demographic development, the prevalence of CHD will increase with 41.9% in the period to 2025. Lifestyle factors play an important role in the development of CHD. Unhealthy nutrition, smoking and physical

[9] In the clinical setting it is called secondary prevention, but in the public health sector the term tertiary prevention is used [1].

inactivity have an unfavourable impact on serum cholesterol level, blood pressure, obesity and coagulation of the blood (Feskens et al., 2006).

3.6.2 Current Situation

In the Netherlands different guidelines exist in the treatment and prevention of a second MI. Firstly, the Dutch multidisciplinary CBO guideline 'Cardiovasculair Risicomanagement' (Cardiovascular Risk Management) (CBO, 2006) advises as pharmacotherapy for patients with CVD a combination of aspirin, antihypertensive drugs (if systolic blood pressure is ≥140 mmHg) and statins (if LDL > 2.5 mmol/l). The CBO guideline and the guideline of the Netherlands Heart Foundation (Revalidatiecommissie NVVC & Hartstichting, 2004) advised as non medicinal therapy: smoking cessation, optimal body weight, sufficient physical activity, reduced saturated fatty acids and salt intake, intake of 200 grams of vegetables and 2 pieces of fruit daily, (fatty) fish 1-2 times a week and moderate alcohol intake. Secondly, there are two clinical guidelines for the promotion of the quality of clinical patient care, used by the Dutch Society of Cardiology (NVVC). One of the guidelines is aimed at patients with acute myocardial infarction without a persistent ST-segment elevation[10], (Bertrand et al., 2002) and the other at patients with ST-segment elevation, based on the European Society of Cardiology (ESC) guidelines (Van de Werf et al., 2003). The 'without persistent ST-segment elevation' describes that it is mandatory that patients quit smoking, that blood pressure control should be optimized, and that lifetime antiplatelet medication, beta-blockers, ACE inhibitors and lipid lowering therapy should be combined. The guideline 'presenting with ST-segment elevation' recommends (combinations of) pharmacotherapy and lifestyle changes to prevent recurrence of cardiovascular events (i.e. tertiary prevention). Life-style changes include smoking cessation and a Mediterranean-type diet. Furthermore, optimal glycaemic and blood pressure control is necessary in specific risk-groups as diabetics and hypertensive patients. Pharmacotherapy comprises combinations of aspirins, oral beta-blockers, ACE-inhibitors and statins. Finally, supplementation with 1 g fish oil n-3 polyunsaturated fatty acid is recommended.

3.6.3 New intervention

The new intervention includes additional dietary supplementation of highly concentrated n-3 polyunsaturated fatty acids (PUFA) at a dosage of 1 g/day, next to the standard treatment in order to prevent a second MI. One capsule of PUFA contains 850-882 eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the average ratio of EPA/DHA 1:2. It should be noted that in this intervention, PUFAs are used as additional drug for those who have had a MI (tertiary prevention), and not as a food supplement for healthy people (primary prevention). Currently, there is discussion about the validity and permissibility of such health claims for enriched foods (a.o. with PUFAs) to prevent CVD (Verhagen et al., 2007).

3.6.4 Effectiveness

There has been a lot of research investigating the effect of supplementation of n-3 PUFAs compared to usual care. The largest study is the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-prevenzione trial (1999). Main conclusion of this study was that dietary supplementation with n-3 PUFA (1 g. daily) led to a clinically important and statistical significant decrease of sudden cardiovascular deaths with 30% (p=0.0242). They used a multicentre, open label design. Weakness of the study is that they compared PUFA with usual care, but statins were not used in

[10] A typical ECG tracing of a normal heartbeat (or cardiac cycle) consists of a P wave, a QRS complex and a T wave. The ST segment connects the QRS complex and the T wave. The normal ST segment has a slight upward concavity.

the usual care at that moment. Nothing is known about the interaction between PUFAs and statins and it was not a blinded trial. A brief review of Harrison & Abhyankar concluded that omega-3 fatty acids play a significant role in the tertiary prevention of post-myocardial infarction. The mechanism of action of omega-3 fatty acids are: prevention of arrhythmias, effect on heart rate variability and blood pressure, decrease platelet aggregation, inhibition of new plaque formation and triglyceride lowering (Harrison & Abhyankar, 2005)[11]. In a review Gebauer et al. also came to the conclusion that for the treatment of existing CVD, 1 g daily intake of omega-3 fatty acids is recommended (Gebauer et al., 2006). The conclusion from a review of Wang et al. was that evidence suggest that increased consumption of n-3 PUFAs from fish or fish-oil supplements reduces the rates of all cause mortality, cardiac and sudden death, and possibly stroke (cerebrovascular disease) (Wang et al., 2006). Von Schacky concluded in his review of large-scale interventions, systematic reviews and meta-analyses, that the omega-3 fatty acids EPA and DHA (Omacor®) protect from sudden cardiac death, fatal and nonfatal myocardial infarction and cardiac arrhythmias. As a consequence, some cardiac societies have incorporated EPA and DHA (Omacor®) for tertiary prevention into their respective guidelines (von Schacky, 2007) .

3.6.5 Cost-effectiveness

The literature search resulted in four economic evaluations of the use of n-3 PUFA for tertiary prevention after myocardial infarction (MI). One of the studies was published in 2001, the other three in 2006. All studies were of good quality and are described in this subparagraph.

Franzosi et al. compared the use of n-3 in addition to the usual care with usual care without addition of n-3 in a randomized controlled trial (RCT) of 11,324 patients. Using average costs and effects and a discount rate of 5%, the costs per life year saved (LYS) were € 24,603 (2006 €: 31,984). In the sensitivity analyses they constructed a best and worst case scenario, using optimistic and pessimistic hypotheses for effectiveness and costs. This resulted in a cost-effectiveness range from € 15,721 per LYS to € 52,524 (2006 €: 20,437 to 68,281) per LYS (Franzosi et al., 2001)[12].

Schmier et al. compared n-3 in addition to the usual care with usual care alone in a decision-analytic model. Double-blind, RCTs that evaluated the effects of omega-3 supplements on cardio vascular diseases were included in the effect estimates. This study included males only. The ICER (costs per MI avoided) were $16,340 (2006 €: 15,360) after one year and was estimated $9,921 (2006 €: 9,326) after 42-months. When estimating the cost per CV death avoided and including productivity costs, the supplementation group dominated the no supplementation group (i.e. more effective and less costly) (Schmier et al., 2006).

Quilici et al. developed a cost-effectiveness model based on the GISSI-P trial, combining a survival and a Markov model, over a life time period. They showed the ICERs (costs per QALY) over a four year period: £ 15,189 (2006 €: 22,480) and over a lifetime: £ 3,723 (2006 €: 5,510). They also showed the costs per LYG. Over four years this ICER was £ 12,011 (2006 €: 17,776) and over a lifetime £2,812 (2006 €: 4,162) (Quilici et al., 2006)[13].

Lamotte et al. did research in five countries: Australia, Belgium, Canada, Germany and Poland. They also compared supplementation with n-3 to the drugs used in usual care versus no supplementation.

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[11] One of the authors works for Solvay Healthcare UK that markets Omacor® in the UK

[12] The study was funded by a research grant from Pharmacia $ Upjohn and Società Prodotti Antibiotica, and was conducted independently by the Instituto di Ricerche Farmacologiche 'Mario Negri". The views expressed are those of the authors.

[13] This study was carried out by Innovus Research (UK) Ltd under a grant from Solvay Pharmaceuticals GmbH. The study was carried out independently by Innovus and the manuscript was approved by each author before submission. Solvay had the opportunity to comment on a draft of the manuscript and the authors were free to decline publication.

Based on the clinical outcomes of GISSI-P, a decision model was built. They showed the ICERs (costs per LYG) over 42 months and over a life-long period. Here we present the ICERs from Belgium and Germany, as these countries resemble the Netherlands the best. For Belgium the ICER over 42 months was € 5,097 (2006 €: 5,300) and over a lifetime € 9,048 (2006 €: 9,410). For Germany the 42 month ICER was € 4,204 (2006 € 4,372) per LYG and the lifetime ICER was € 8,315 (2006 €: 8,648) (Lamotte et al., 2006b)[14].

3.6.6 Transferability

The economic evaluations described above were conducted in multiple countries, including neighbouring countries as Belgium and Germany. Compared to these countries, CHD mortality is relatively low in the Netherlands. Because there are no big differences in the quality of care, it is expected that the incidence is lower too. The quality of cure and care is almost the same in West-European countries. The total number of coronary artery bypass grafts (CABG) and percutaneous transluminal coronary angioplasties (PTCA) are in the Netherlands around the European average. The use of pacemakers' in neighbouring countries like Belgium and Germany is higher than in the Netherlands (Van der Wilk et al., 2006a). In the multi-country economic evaluation, referring to Belgium and Germany, the costs of pacemakers were not included in these studies. The costs of CABG and PTCA are almost equal in Germany and the Netherlands; in Belgium they are more expensive. The costs of Omacor® are equal in Belgium and the Netherlands, but a little bit higher in Germany. Based on these considerations, no major problems with transferability are to be expected for n-3 faty acids.

3.6.7 Implementation

ZonMw-projects
On this subject ZonMw did not commission any research.

Relevant policy documents and guidelines
The assessment of the implementation aspects is based on Dutch guidelines and reports concerning cardiovascular diseases and/or nutrition:

- Multidisciplinary guideline Cardiovascular Riskmanagement by the Dutch Institute for Healthcare Improvement (CBO) (2006).
- Guidelines on Healthy Nutrition by the Dutch Health Council (2006).
- Guidelines on Coronary Heart Rehabilitation (Netherlands Heart Foundation/Dutch Society of Cardiology (2004).
- Report *Omega-3-vetzuren (Omacor)* (CFH-report 04/13) by the Dutch Health Care Insurance Board (CVZ) (2004).
- An explorative study *What shall we eat?* on challenges for research into nutrition and health in the Netherlands, by Wageningen University and Research, ZonMw, RIVM en TNO (2007).

Innovation
In the Dutch guidelines the main recommendation about the consumption of (fatty) fish is: 1-2 times a week (CBO, Netherlands Heart Foundation, Health Council).

[14] The study was carried out by HEDM-IMS under an unrestricted grant from Solvay Pharmaceuticals GmbH. The study was performed independently by HEDM-IMS, and the manuscript was approved by each author. Solvay had the opportunity to comment on a draft of the manuscript and the authors were free to decline publication. York Zoellner contributed to the report review, and is a Solvay Pharmaceutical employee.

The Netherlands Heart Foundation is reserved about PUFA-supplements for heart patients and for the general population because of insufficient evidence. The Netherlands Heart Foundation is also reserved about advises to consume nutrition enriched with PUFA. They advise it only as an alternative for fish for people who do not like eating fish.

The Heart Foundation supports ongoing research into consumption of nutrition enriched with PUFA ('Alpha-Omega' trial). Results are expected in 2010. Research on the working mechanisms of PUFA related to cardiovascular diseases is also still going on ('Sofa'-trial). More knowledge must be generated on the effectiveness and preventive mechanisms of PUFAs.

User groups
Main user groups are general practitioners, cardiologist, internists and dieticians. However, most health practitioners often do not offer their patients adequate advice based on the guidelines. One of the reasons could be that recommendations on nutrition do not fit within the Dutch culture. Not all physicians are able or willing to advise positively on nutrition habits ('personal business'). With respect to supplements, there is still a lot of scientific research necessary into the question whether a healthy diet can be added or replaced by supplements (report *What shall we eat?* 2007).

Considering the end users, it appears that the average consumption of (fatty) fish in general is lower than the recommended 1-2 times a week (Revalidatiecommissie NVVC & Hartstichting, 2004). Therefore, PUFA-supplements could be a solution for people who do not like fish. However, the Netherlands Heart Foundation is reticent about the supplements.

Resources
PUFA-supplements are available over the counter (self care-product). In 2004, the Dutch Health Care Insurance Board advised the Minister of Health not to include PUFA-supplements (Omacor®) into the 'Geneesmiddelen Vergoedingen Systeem' (GVS) for treatment of patients. As a consequence, health insurers will not reimburse PUFA-supplements, which will hamper its implementation. A political debate is necessary to decide whether PUFA is regarded as medical drug or a 'lifestyle/self care product'.

Organization
User groups are informed about the knowledge for the present guidelines, and they keep up with new developments.

Conclusion
Recommendations for PUFA-supplements in the guidelines are not to be expected soon, because research on working mechanisms of the preventive effect of PUFA, and their advantages and disadvantages is still going on. Furthermore, a change of culture and opinion on the position of PUFA in healthcare and disease prevention (appreciation as a medical drug or a self care-product) among policy makers and healthcare professionals is required before (positive) recommendations on supplements can be implemented.

Dimension	Innovation	User groups	Resources	Organization
Score*	1-2	2	1	2

* Vis-score: a scale for measuring implementation potential

3.6.8 Conclusion

Before general practitioners and cardiologists can decide about including recommendations of PUFA supplements in their guidelines, more knowledge is required (harms and benefits of supplements, effectiveness and preventive mechanisms of action of PUFA). A lot of research to the effects of PUFAs

is going on at this moment (von Schacky, 2007). Furthermore, a change of culture and attitude among policy makers and caregivers is required to implement recommendations on supplements.

Table 6. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
*	*	**	*

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

3.7 Lifestyle intervention to prevent diabetes mellitus

3.7.1 Health problem

In 2003 almost 600.000 people had diabetes mellitus in the Netherlands: 290.000 men and 310.000 women (estimation based on general practitioners registrations). In that year 36.300 male and 36.200 female new cases were estimated. The total number of patients with diabetes, both type 1 and type 2, has increased since the second part of the 1990. The costs of diabetes were € 735 million in 2003, representing 1.3% of the total heath care spending in the Netherlands (Baan, 2005; Poortvliet et al., 2007).

Risk factors for the development of type 2 diabetes are a family history of diabetes, overweight or obesity, an abdominal fat distribution, lack of physical activity, smoking and unhealthy nutritional behaviour (Poortvliet et al., 2007)

Based on demographic development an increase in the absolute total number of persons with diabetes mellitus of 32.5% between 2005 and 2025 is expected (Baan, 2005); (Poortvliet et al., 2007). Taking into account a continuing increase in the prevalence of obesity, and increasing incidence rates, the prevalence of diabetes mellitus probably will be much higher.

Impaired Glucose Tolerance (IGT) is the preliminary stage of type 2 diabetes mellitus. The main risk factors of IGT are similar to diabetes, overweight or obesity and lack of physical activity. IGT is diagnosed when the 2-hour glucose concentration is between 7.8 and 11.1 mmol/l, together with a fasting glucose concentration < 7.8 mmol/l (de Vegt et al., 2001). The prevalence of IGT is unknown, but a recent estimation, based on the Hoorn-study (2003) for a population of 60 years and older showed prevalence rates of 30.2% among men and 29.1% among women. From people with IGT, about 40% will develop type 2 diabetes (de Vegt et al., 2001).

3.7.2 Current situation

The Dutch CBO guideline for early diagnosis and treatment of obesity is in development and will be present in 2007. A new guideline for general practitioners for diabetes has been published in 2006 (Rutten et al., 2006); (Bouma et al., 2006). In this guideline, it is recommended that the general practitioner (GP) advises IGT-patients on smoking cessation, increasing physical activity, healthy diet and weight loss if the body mass index ≥ 25 kg/m². However, except for advice, the GP does not offer any lifestyle intervention. According to this guideline, IGT-patients should be controlled by the GP every three months. When the lifestyle advice does not succeed in normalising blood glucose concentration, the GP prescribes pharmacotherapy. The first option is metformin, to lower the blood glucose concentration.

3.7.3 New intervention

The intervention is a lifestyle program consisting of a healthy diet (every three months a visit to a dietician) in combination with a physical activity program (at least 1 hour/week an exercise session, guided by a trainer). People at risk for type 2 diabetes mellitus are the target group.

3.7.4 Effectiveness

The Diabetes Prevention Program (DPP) demonstrated in a randomized controlled trial (RCT), including 3234 persons, that both intensive lifestyle and metformin interventions reduced the incidence of diabetes compared with a placebo intervention. The lifestyle intervention was more effective than metformin (Knowler et al., 2002). The estimated cumulative incidence of diabetes at three years follow-up was 14.4% in the lifestyle intervention group, 21.7% in the metformin group and 28.9% in the placebo group. The key aspects of the DPP lifestyle protocol were (DPP, 2002):

- clearly defined weight loss and physical activity goals;
- individual case managers or 'lifestyle coaches';
- intensive ongoing intervention (initial core curriculum to achieve standardization of the intervention, supervised exercise sessions offered at least two times per week throughout the trial, a flexible maintenance program with supplemental group classes, motivational campaigns and restart opportunities);
- individualization through a 'toolbox' of adherence strategies;
- materials and strategies that addressed the needs of an ethnically diverse population;
- an extensive local and national network of training, feedback and clinical support.

The 'Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM)' was a Dutch RCT, that included 88 subjects with IGT (2003; (Mensink et al., 2003a). The intervention program consisted of a lifestyle program on diet and physical activity according to general recommendations (Dutch guideline for a healthy diet, Dutch Nutrition Council, 1992 and the American College of Sports Medicine, (ACSMPS, 1998). Subjects were stimulated to increase their physical activity. In addition to counselling sessions, participants were encouraged to participate in an organised fitness program. This program consisted of a combination of resistance training, and aerobic exercise training. Furthermore, participants were encouraged to stop smoking and, if necessary, to reduce alcohol intake. Reduction of the body weight after 1 year was significantly larger in the intervention group as compared to the control group ($P < 0.01$). After one year the 2 hours glucose concentration was decreased with 0.8 mmol/l in the intervention group (95% CI -1.3, -0.2) compared to an increase of 0.2 mmol/l (95% CI -0.4, +0.8) in the control group (p-value for differences in change between groups <0.05). After 2 years the 2-hours plasma glucose concentration declined to 8.0 mmol/l (± 0.4 mmol/l) in the intervention group and increased in the control group with 0.8 mmol/l (± 0.4 mmol/l), p-value for differences in change between groups <0.01 (Mensink et al., 2003c); (Mensink et al., 2003a). Fasting insulin concentration was 2.5 mU/l lower after 1 year in the intervention group compared to a slight increase of 0.4 mU/l in the control group (P-value for difference in change < 0.01). In conclusion, the results of this study showed that lifestyle intervention improved the glucose tolerance, even in a less obese and more physically active population. Furthermore, the results underscored the importance of combining diet and physical activity to improve glucose tolerance and insulin resistance (Mensink et al., 2003b; Mensink et al., 2003c). The follow-up of the Finnish Diabetes Prevention Study (Lindstrom et al., 2006) showed that during the total follow up of 7 years, the incidence of diabetes was 4.3 and 7.4 per 100 person-years in the intervention and control group, respectively (p=0.0001), indicating 43% reduction in relative risk. Lifestyle intervention in people at high risk for diabetes resulted in sustained

lifestyle changes and a reduction in diabetes incidence, which remained after the individual lifestyle counselling, was stopped.

3.7.5 Cost-effectiveness

Six economic evaluations about lifestyle interventions for the prevention of diabetes were found and are all of sufficient quality to be included in this report. One of these was carried out in the Netherlands (Jacobs-van der Bruggen et al., 2007). The studies, except the Dutch one, compared lifestyle intervention with metformin and with a placebo intervention. Five studies took the effect data from the DPP (Knowler et al., 2002). The Dutch study (Jacobs-van der Bruggen et al., 2007) had expressed potential intervention effects within a range that reflects the diversity of positive intervention effects found in the international literature. In this study the intervention was compared with no intervention. All studies were of good quality and described either cost-effectiveness or cost-utility.

In 2003, the Diabetes Prevention Program Research Group performed a within-trial cost-effectiveness study (DPPRG, 2003) using the costs associated with the program (Herman et al., 2003). From a health system perspective the ICER (costs/case of diabetes prevented) of a lifestyle intervention versus placebo was U.S. $ 15,655 (2006 €: 15,812) (ICER metformin versus placebo: U.S. $ 31,338=2006 €: 31,651).

In 2005 Herman et al. described in a lifetime modelling study the cost-utility of intensive lifestyle modification. An incremental cost-utility ratio was calculated to combine the costs and benefits of the DPP interventions. The incremental cost per QALY was U.S. $ 1,124 (2006 €: 1,135) with intensive lifestyle modification over placebo (metformin over placebo: ICER: U.S. $ 31,286=2006 €: 31,598, big difference caused by much less QALYs gained). Intensive lifestyle modification dominated metformin, i.e the former was more effective and less costly than the latter (Herman et al., 2005).

Palmer et al. described in a lifetime modelling study the economic implications of the DPP in Australia, France, Germany, Switzerland and the U.K.. Except for the U.K. (where a small increase in costs was seen in the treatment groups versus controls), both the intensive lifestyle program and metfomin dominated the placebo intervention in costs per life year gained. The intensive lifestyle program dominated metformin, meaning that the intensive lifestyle program was less costly and more effective (Palmer et al., 2004).

The study of Caro et al. showed that in Canada, comparing lifestyle modification with meformin, the cost per life year gained was Can $ 7,252 (2006 €: 5,584), which means that the lifestyle intervention was more effective but had higher costs. Comparing with no treatment, the ICER was Can $ 749 (2006 €: 577) (Caro et al., 2004).

A recent Dutch study by Jacobs-van der Bruggen et al. concluded that health care interventions for high risk groups and community based lifestyle interventions targeted to the general population (low risk) are both cost-effective ways of curbing the growing burden of diabetes. They used the National Institute for Public health and the Environment (RIVM) Chronic Disease Model. The ICER (costs per QALY) for the community intervention (low risk) was € 3,900-3,100 (2006 €: 3,939-3,131) and for the health care intervention (moderate risk of developing diabetes=obese adults 30-70 years) was € 5,500-3,900 (2006 €: 5,555-3,939). The costs in this study were based on two Dutch projects. The community based program ‘Hartslag Limburg (Heart Health Limburg)’ and the ‘SLIM’ study, as mentioned above (Jacobs-van der Bruggen et al., 2007).

Icks et al. recently presented results from their economic evaluation, using data from the KORA Survey and the DPP. The ICER (cost per case prevented) for lifestyle improvement versus no intervention was € 4664 (2006 €: 4,851) from the third party payers perspective. The ICER of the lifestyle intervention versus metformin was €415 (2006 €: 432) (Icks et al., 2007).

3.7.6 Transferability

Both an effect study and an economic evaluation were Dutch, so no problems are expected by transferring the results and recommendations for this study. Also included is a multi-country study with four west-European countries (Palmer et al., 2004). In all of these countries a lifestyle intervention is cost-effective. The Dutch study used the discounting rates of 4% for costs and 1.5% for effects, recommended in the Netherlands (CVZ, 2006).The other studies used discounting rates of 3% and more for both costs and effects. Taking this into account the ratios will be more favourable transferred to the Dutch situation when lower discount rates for effect were used.

3.7.7 Implementation

ZonMw projects

Two projects on the impact of lifestyle interventions in subjects with impaired glucose tolerance (IGT) are currently carried out. One is about the long term effects of changes in lifestyle on glucose tolerance and adherence to the intervention programme in subjects with IGT, wich is in fact the extension of SLIM to intervention duration of 6 years, and a total number of 147 subjects The final results of this project are expected in December 2007. From the recently reported data it is clear that the intervention (changes in lifestyle) improves the glucose tolerance and decreases the cumulative incidence of diabetes. The cost effectiveness has been calculated (RIVM chronic disease model) to be 3900 euro per QALY (Jacobs-van der Bruggen et al., 2007) .

A second project started only recently, and no results are available yet. This project will study the implementation of a concept for active primary prevention of diabetes mellitus type II (DM II) in a primary care setting. The intervention will imply adjustment of lifestyle and diet of individuals with IGT, based on the SLIM protocol It aims at a moderate weight loss, increased daily physical exercise, and improvements in dietary intake of fats and/or fibers. The project will evaluate the application of some of the findings from the first mentioned study in a primary care setting. Participants will be followed/monitored for 2.5 years.

Moreover, all lifestyle projects at the Prevention programme add to the knowledge about dealing with IGT.

Relevant policy documents, reports and guidelines

A number of professional bodies in the Netherlands focus on the prevention and care of diabetes. Patientsgroups are active and ZonMw has a special Diabetes programme aiming at diabetes management and education/empowerment of diabetes patients (www.zonmw.nl/diabetes). Prevention of DM II is one of the priorities of the Ministry of Health, Welfare and Sport. In the recent letter from the Dutch government (*Visie op gezondheid en preventie*, september 2007) the importance of lifestyle (physical exercise and balanced diet) was emphasized for the prevention of diabetes (IGT) and cardiovascular diseases. Also the Council for Public Health and Health Care (RVZ) identifies 'Prevention of Diabetes type II focused on high-risk groups' as a priority in her report *Fair and sustainable care* (October 2007). Professional bodies and the Diabetes Federation (NDF) have developed Diabetes guidelines. As IGT precedes diabetes in many documents on diabetes, also IGT is (marginally) mentioned:

- Reports of the Dutch Health Council: Overweight and Obesity (2003) and Screening for type 2 Diabetes (2004).
- Multidisciplinary guideline Cardiovascular Riskmanagement by the Dutch Institute for Healthcare Improvement (CBO).
- Guidelines by the Dutch College of General Practitioners on type 2 diabetes mellitus and Cardiovascular risk management.

– In December 2006 a *Systematic Review of (cost)effectiveness of lifestyle interventions for people with impaired glucose tolerance or type 2 diabetes mellitus in combination with obesity (Riemsma, Clar, Nixon, Kleijnen)* was published. (www.systematic-reviews.com)

Innovation
Guidance to improve impaired glucose tolerance are similar to the one to prevent type 2 diabetes. More physical exercise is the most important guideline, together with a balanced diet; a (small) reduction in weight is often the result. The expectation is that early diagnosis of IGT, followed by a change in lifestyle can postpone and may even prevent development of type 2 diabetes.

The results of the above mentioned ZonMw project show that the lifestyle intervention improves the glucose tolerance and decreases the cumulative diabetes incidence. The lifestyle programme developed in this project can be used by the ministry, local authorities, homecare institutions, practitioners and other (private) parties.

Many lifestyle programmes are available. Positive results, i.c. prevention of type 2 diabetes, have been published.

User groups
User groups include the risk groups of people with IGT and/or overweight/obesity, and people (originally) from Asia, and older people (50 and above). Main user groups among the caregivers are general practitioners, municipal health services, physicians (first and second line), and public and private organisations offering lifestyle programmes. The most important policy makers are the Ministry of Health, Welfare and Sport (VWS), Dutch Health Care Insurance Board (CvZ), and the Health Council of the Netherlands.

Resources
Lifestyle programmes are not very expensive. Some health insurance companies already pay (partly) for the cost of a physical exercise programme.

Organisation
Relevant guidelines exist, but not all professionals follow these 'rules'. An opportunity for the intervention is that a healthy lifestyle is already promoted for many years and for more reasons than IGT or DMII prevention alone. Spin off may be improvement of glucose tolerance and prevention of DMII. However, an important barrier is that most people know that more exercise and a better diet improves their health and decreases the chance of getting illnesses or to die. But changes in lifestyle are difficult. During the lifestyle programmes regular contact with professionals is necessary to help people 'keep on going'. Compliance is a very important factor to achieve results of lifestyle programmes. It influences the level of cost-effectiveness too.

Conclusion
Evidence based lifestyle interventions (exercise plus diet) are highly recommended for people with IGT to prevent development of diabetes. As policymakers and healthcare workers give much attention to the prevention of diabetes/IGT ('hot topic') the implementation potential is high.

Dimension	Innovation	User groups	Resources	Organisation
Score	3	3	3-4	2-3

*VIS-score; a scale for measuring implementation potential

3.7.8 Conclusion

Based on demographic development an increase in the absolute total number of persons with diabetes mellitus of 32.5% is expected between 2005 and 2025. The international health economic literature shows the effectiveness and the cost-effectiveness of a life-style program in the prevention of diabetes mellitus compared with either metformin or no intervention. A Dutch economic evaluation presents an ICER for the community intervention (compared with no prevention) between € 3,900-3,100 and for the health care intervention between € 5,500-3,900, both far below the Dutch threshold of € 20,000 per QALY that is often used. The main conclusion of Icks et al. was, that before implementing the programme, efforts should be made to improve patient participation in order to achieve better clinical and cost-effectiveness of prevention of diabetes in 'real world' clinical practice (Icks et al., 2007). In their report 'Rechtvaardige en duurzame zorg' (Fair and sustainable healthcare), the Council for Public Health and Health Care recommends to reimburse life-style programs in the prevention of diabetes mellitus (RVZ, 2007). Health care professionals have to be advised to use the guidelines strictly.

Table 7. Appraisal of aspects of the intervention[1]

Effectiveness	Cost-effectiveness	Transferability	Implementation
**	**	**	**

[1] one star indicates moderate/unfavourable, two stars indicate strong/favourable

4 Discussion

4.1 Main findings

Seven preventive interventions that are currently not systematically implemented in the Netherlands, and that have favourable cost-effectiveness were described in this report (Tables 9 and 10). Five interventions fall in the domain of disease prevention, and two interventions are lifestyle interventions. No health protection intervention was included.

Table 8. Included interventions

Disease	Intervention	Targetgroup	Chapter
Gastric disorders	Screening (*H. pylori* infection)	Middle-aged population	3.1
Influenza	Vaccination	Healthy children	3.2
Osteoporosis	Screening (bone densitometry)	Women (≥ 70 years)	3.3
CVD	Aspirin use	General population	3.4
Falls	Exercise program	Indep. living elderly	3.5
Recurrent MI	PUFA	Patients with MI	3.6
Diabetes mellitus 2	Lifestyle intervention	People with IGT	3.7

Table 9. Appraisal of aspects of included interventions

Intervention	Effectiveness	Cost-effectiveness	Transferability	Implementation
H. pylori screening	*	*	*	*
Influenza vaccination	*	*	**	*
Osteoporosis screening	*	*	*	*
Aspirin use to prevent CVD	**	**	**	*
Exercise to prevent falls	**	**	**	*
PUFAs to prevent recurrent MI	*	*	**	*
Lifestyle interv. to prevent DM2	**	**	**	**

4.2 Discussion

Included interventions

The vast majority of the identified preventive interventions that seem cost-effective based on at least three economic evaluations are in the domain of disease prevention (vaccination, screening, prophylaxis). This is in line with the conclusion of our latest report (De Wit et al., 2007). Only two interventions can be considered as health promotion intervention, and none of the interventions was in the domain of health protection. Again, it should be stressed that the absence of health promotion and health protection is because of a lack of cost-effectiveness analyses in these domains, and not because such interventions were less cost-effective. The paucity of these analyses may be attributed to the fact that the economic evaluation of health promotion interventions generally requires complex cost-effectiveness models with assumptions about the translation of intermediate effects of interventions to long term effects as morbidity and mortality (De Wit & Brouwer, 2004). Also, evaluation in the health promotion field traditionally takes the form of process evaluations, instead of effect evaluations.

Moreover, cost-effectiveness evidence does not play a formal role in decision making about health promotion campaigns or programs. Although this also applies to decision making regarding disease prevention interventions, traditionally there is much more focus on cost-effectiveness in e.g. vaccination or screening programs. This may be related to the higher financial impact of vaccination and screening programs, compared to health promotion programs.

Effectiveness

Only three of the seven included interventions have a conclusive evidence-base for effectiveness of the intervention. All other interventions have some uncertainty about their effectiveness. Some interventions only have evidence on intermediate outcomes and not on e.g. mortality reduction. Other interventions only have evidence from retrospective studies but not from controlled trials. Apparently, the absence of a convincing evidence-base for the effectiveness of a preventive intervention does not restrain some researchers from modelling the potential cost-effectiveness of such an intervention. For instance, although the ECDC concluded that there is not enough evidence to implement routine vaccination of healthy children against influenza (ECDC, (ECDC, 2007), more than five recent economic evaluations conclude that this would be very cost-effective. Taking a closer look at the evidence regarding the effectiveness of this vaccination shows that there is indeed no trial-based evidence for vaccinating healthy children below two years of age. There is only evidence from a few retrospective studies.

Based on this observation, we conclude that in future reports we should include only those interventions that are effective, based on a high level of evidence. To make this explicit, we should give every intervention in the pre-selection a ranking based on the level of evidence-classification as for instance used by the Dutch Institute for Healthcare Improvement (Kwaliteitsinstituut voor de gezondheidszorg CBO) (see Table 10) (CBO, 2007). We may for instance include 'having level 1 or 2 evidence for effectiveness of the intervention' as an extra inclusion criterion. Reporting all interventions that were excluded for this reason, will make this year's observation that many cost-effective interventions have unknown effectiveness more visible.

Table 10. levels of evidence

Level of evidence	Conclusion based on
1	Systematic review, or two or more RCTs
2	One RCT, or two or more comparative studies
3	One comparative or non-comparative study
4	Expert opinion

Implementation

In previous reports, the implementation potential was assessed in a narrative way, summing the most important barriers and opportunities for future implementation in the Netherlands. This was the first year in which the assessment of the implementation potential of the identified interventions was based on an instrument that more systematically addressed the four relevant aspects of implementation: innovation, user-groups, organisation, and resources. Although it was difficult to give each aspect a ranking between one and five, and to create an end score for each intervention, the structure of systematically assessing these four items was very helpful to make the assessment of the implementation potential more objective. As can be seen from Table 9, only one intervention was favourable evaluated with regard to its implementation potential. For some interventions this is related to the absence of conclusive evidence concerning effectiveness. Two other interventions have favourable effectiveness, cost-effectiveness, and transferability, but still have low VIS-scores. Concerns about compliance and side-effects were important barriers for these interventions.

Cost-utility
Although CUA has become the recommended method of economic evaluation (CVZ, 2006), still most of the published economic evaluations are CEAs instead of CUAs. In this report, about one in three of the included studies was a CUA. However, the proportion of economic evaluations that is a CUA is growing (see Figure 2 in the introduction). So, costs per QALY models are becoming more and more the standard method of economic evaluation. As a consequence of this development, the cost-effectiveness of different interventions becomes more comparable among each other. For instance, if for both interventions high-quality CUAs are available, it will be possible to see if a lifestyle program (primary prevention) provides more value for money than a screening program (secondary prevention), or the other way around. Such information can be helpful for policy makers in making decisions about what interventions to implement or reimburse. However, such comparisons are conditional on the application of similar CUA-methods. Despite the availability of guidelines for the execution of CUAs, this is often not the case.

Two in three of the included economic evaluations are CEAs. Almost half of these CEAs used LY gained as outcome measure, and almost 40% calculated costs per case prevented. Costs per LY gained is already a more general measure than cases prevented. However, LY gained still only concerns the *mortality* reduction due to a certain intervention. Thus, the costs per LY gained of an intervention that prevents a disease that primarily causes morbidity is not comparable to the costs per LY gained of an intervention that prevents a disease that primarily causes mortality. This emphasized the importance of using an outcome measure that combines effects on both quality and quantity of life.

Societal perspective
It appeared that only approximately one in three studies used the societal perspective; all other studies included only direct medical costs (i.e. the health care perspective, or the third payer's perspective). This is remarkable because many guidelines for economic evaluations recommend to include all direct and indirect costs of an intervention (i.e. the societal perspective) (CVZ, 2006). This may be related to the fact that measuring, for instance, the effects of an intervention on productivity losses, is more difficult than measuring medical costs only. Moreover, very often there is a lack of data about the extent of disease related productivity losses caused by a certain disease. Nevertheless, only including productivity losses in an economic evaluation is a very limited interpretation of the societal perspective. A CEA or CUA from a real societal perspective includes *all* effects and *all* costs directly or indirectly caused by or associated with the intervention. In such an analysis, aspects like the influence of disease or treatment on family caregivers, and long term influence on pension funding should play a role too. Such true societal analyses are still very scarce. However, there is an increasing interest in the societal costs of disease, especially the potential savings of prevention to society through decreased productivity losses. Next year, we plan to introduce some societal costs and effects (e.g. productivity losses) in our cost-utility model of the prevention of depression. This model has been developed within the scope of this project too (Van Baal et al., 2008).

Existing preventive interventions
It is not only important to evaluate the cost-effectiveness of new preventive interventions, but it is also important to evaluate the cost-effectiveness of existing preventive interventions. Firstly, for many preventive interventions the cost-effectiveness is unknown. These interventions or programs were implemented without an a priori economic evaluation. Secondly, those interventions that were implemented based on cost-effectiveness evidence, may have become less or more cost-effective over the years. Learning effects, or changes in incidence of the disease, in the costs of the preventive intervention or the costs of care for those with the disease, in the organisation, or in the use (adherence) of the intervention may change the incremental cost-effectiveness of an intervention over time. Therefore, for 2008 the Ministry of Health, Welfare, and Sport asked us to make an exploration of the

available evidence on the cost-effectiveness of a number of preventive interventions or programs that are at present usual care in the Netherlands.

Cost-ineffective preventive interventions
The current project only included interventions that appear cost-effective. Information on interventions with poor cost-effectiveness was not reported. However, it is also important for policy makers to know what interventions should be withdrawn, or should not be implemented because of their high costs in relation to the effects. So, in the coming years, it would be useful to report interventions that seem cost-ineffective in one or more economic evaluations.

Conclusion
To conclude, despite the increasing interest in prevention, and health promotion in particular, relatively little is known about its cost-effectiveness. Therefore more attention should be paid that studies investigating the effectiveness of health promotion also include a cost analyses, facilitating cost-effectiveness analyses. Among others, the RIVM has developed a model (chronic disease model, CDM (Van Baal et al., 2008)) that can be used to estimate the impact of a health promotion programs on chronic diseases, mortality, quality adjusted life years and health care costs. The use of this or similar other chronic disease models may stimulate higher quality economic evaluations in the health promotion field.

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List of abbreviations

ACIP	advisory committee on immunization practices
AOM	acute otitis media
BCR	benefit to cost ratio
BMD	bone mineral density
CABG	coronary artery bypass grafts
CBA	cost-benefit analysis
CBO	Dutch Institute for Healthcare Improvement
CBS	Centraal Bureau voor de Statistiek
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CUA	cost-utility analysis
CVA	cerebrovascular accident
CVD	cardio vascular disease
CVZ	College voor Zorgverzekeringen
DEXA	Dual-energy X-ray absorptiometry
DHA	docosahexaenoic acid
DPP	diabetes prevention program
ECDC	European Centre for Disease Prevention and Control
EPA	eicosapentaenoic acid
GERD	gastro-esophageal reflux disease
GISSI	Gruppo Italiano per lo Studio della Sopavvivenza nell' Infarto miocardico
GP	general practitioner
ICER	incremental cost-effectiveness analysis
IGT	impaired glucose tolerance
ILI	influenza-like illnesses
LYG	life year gained
LYS	life year saved
MI	myocardial infarction
NET	net present value
NHG	Dutch General practitioners Society
NNS	number needed to screen
OECD	Organisation for Economic Cooperation and Development
PTCA	percutaneous transluminal coronary angioplasties
PUFA	polyunsaturated fatty acid
ROC	Receiver Operator Characteristic
SD	standard deviation
SLIM	Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht
QALY	quality adjusted life year
QOL	quality of life
RCT	randomized controlled trial
RVZ	Raad voor de Volksgezondheid en Zorg
SOYF	stay on your feet
USPSTF	U.S. Preventive Services Task Force
WHO	World Health Organisation

rivm

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Appendix 2: VIS-score

VIS-score*

Score	Innovation	User groups	Resources	Organization
1	The development has been stopped; or no new knowledge is available for further development.	No user groups have been identified for whom the new knowledge would be relevant.	At present, there is no opportunity to finance the further development of knowledge or its implementation.	There is no organisation where the knowledge can be deloped further, or where the change can be introduced.
2	New knowledge is available for further development, which may eventually lead to changes.	There are relevant user groups outside the field of researchers, who have access to the new knowledge.	Resources are made available for the further development of knowledge.	The organisation which can use the new knowledge is informed about the development.
3	New knowledge has been developed into a concept, of which the added value compared to current practice has been proven.	User groups show interest, and are involved in the development of the new concept.	Resources are made available for the further development and testing of the the new concept.	The organisation is involved in the development of the new concept, and has the intention to adapt to its accompanying changes.
4	The concept has been adapted to the situation in practice, and is suited for trial implementation.	User groups have positive experiences with the innovation and its accompanying changes.	Resources are made available for the trial implementationn of the innovation.	The organisation is experimenting with the innovation, and it is satisfied with the results.
5	The innovation has proven to have an added value in practice, and has been made suitable for structural use.	User groups are willing to act according to the innovation and new procedure.	Resources are structurally available to maintain the innovation.	The organisation is ready to introduce the innovation.

* Method used for the assessment of implementation potential by the Netherlands Organisation for Health Research and Development (ZonMw)

Appendix 3: Background tables

Population screening for Helicobacter pylori to prevent gastric disorders

Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Leivo	2004	Finland	15-45 yr 45 yr	€ 437 per infection Cost-saving	The results were sensitive to: probability of *H. pylori* related gastric cancer, costs of screening and GP visit	
Roderick	2003	UK	40-49 yr	€ 9,376 per LY	The sensitivity analysis showed that only when a high opportunistic eradication rate, and a long time lag were assumed, the program became cost-ineffective	The model assumed a time lag before eradication becomes effective. This made the cost-effectiveness less favourable, but it is more realistic that a fixed efficacy.
Mason	2002	UK	40-49 yr	Dominant	The two most important factors in the sensitivity analysis were: efficacy of eradication in reducing dyspepsia costs, and in preventing ulcer and cancer related mortality	Even the worst case scenario costed less than € 24,000 per LY
Fendrick	1999	US	40 yr	€ 7,141 per LY	The results were sensitive to changes in the assumed gastric cancer risk reduction.	Screening plus confirmatory testing resulted in an ICER above € 20,000 per LY.
Sonnenberg	1998	US		€ 13,110 per LY	The ICER was most sensitive to: prevalence of gastric cancer, costs of treatment, effectiveness of eradication	
Parsonnet	1996	US	50 yr	€ 29,250 per LY	The estimate was most sensitive to the effectiveness of eradication on gastric cancer	

Universal influenza vaccination of children

Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Marchetti	2007	Italy	0.5-4 yr	Cost-saving - € 10,700 per QALY	Findings were sensitive to the assumed house hold protection rate, and vaccine effectiveness.	The vaccine effectiveness in children below 2 years of age was based on one retrospective study.
Navas	2007	Spain	3-14 yr	cost-saving	Sensitive to vaccine price and costs of work absenteeism.	Effects of vaccination on non-vaccinated parents and siblings were not included in the model.
Salo	2006	Finland	0.5-13 yr	cost-saving	Vaccination was cost saving in all variations of the probabilistic sensitivity analysis.	
Prosser	2006	US	0.5-2 yr 2 yr 3-4 yr >5 yr	€ 11,640 per QALY € 17,460 per QALY € 27,160 per QALY >€ 79,000 per QALY	ICERS were sensitive to attack rate, and to less extend to hospitalization rate, vaccine effectiveness, and total vaccination costs.	The projected benefits decreased as age increased.
Skowronski	2006	Canada	0.5-2 yr	€ 97-115 per averted case	ICER was sensitive to attack rate, hospitalisation rateAR, HR, and costs of hospitalization	
Meltzer	2005	US	0,5-14 yr	Vaccine break even price: € 30-61	The estimates were relatively sensitive to changes in probability of death, and to the rate of outpatient visits	Indirect costs (i.e. time lost to looking after sick children) were the most important element of the net costs or savings

Universal bone densitometry screening of women aged 70 years and older

First Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Mobley	2006	USA		Screening and treatment (alendronate) vs. no screening and no treatment: €69,233 per QALY	Negative effect on the ICER when less favorable RRs for fractures are used, a high fracture growth rate and by changing the discount rate to 5%. Positive effect by: effects remain longer than 3 years and a discount rate of 0%.	
Schousboe	2005	USA		Screen and treat vs. no screen	1. Univariate sensitivity analyses: moderate increase of the ICER when fracture cost ↓, discount rate ↑ and screening costs ↑	
			65 years	€43,000 per QALY	2. Probalistic sensitivity analyses: 85 y. 99% the ICER was less than €50,000	
			75 years	€5,600 per QALY		
			85 years	dominant		
			95 years	dominant		
Schott	2007	France	Women 70 years and older	1. at risk vs. no screening: €8,539	Sensitive to the number of cycles in the model, costs of a nursing home, probability having a BMD below -2.5, costs of treatment costs of DEXA	
				2. all women vs. no screening: €4,362	'Screen all' was persistently more cost-effective	
Schwenkglenks	2007	Switzerland		Screen and treat vs. no screen	Parameter changed influence the ICER, but the ICER remained below the threshold	In the model input also the 'Rotterdam study'.
			65 years	€6,309 per QALY		
			75 years	€29,432 per QALY		

Low-dose aspirin in the primary prevention of cardiovascular disease

First Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Franco	2007	Dutch	Men	Aspirin vs. smoking cessation	The order of the results was not altered when the costs of adverse events were taken into account for aspirin treatment	At population level antihypetensives are dominated by aspirin treatment
			Moderate risk 60 years	€16,431 per LYS		
			High risk 50 years	€9,709 per LYS		
			High risk 60 years	€7,502 per LYS		
Lamotte	2006	UK, Germany, Spain, Italy	Men and women annual risk 1,5% and max risk on stroke and GI	Aspirin vs. no aspirin; dominant	Monte Carlo analysis based on an annual risk of 1,5%,1%, 0,6% aspirin is dominant in 97,3, 97,2, 97,2% UK, 97,7, 98,7, 97,1% Germany, 98, 97,1, 97,8% Spain and 98, 96,2 and 59,7% Italy	Based on the results of this health economic evaluation in four European countries, low-dose aspirin therapy could be recommended in the primary prevention of CVD in all individuals who have at least a 0,6% per year risk of CHD.
Annemans	2006	UK, Germany, Spain, Italy	Men and women annual risk 5%, 4%, 3%, 2%	Aspirin vs. no asprin,: UK, Germany, Spain: dominant	Probalistis sensitivity analyses: 90% of patients at 10-years risk of 4% and 5% in the four counties: dominant	Patients at low risk of a cardiovascular event, the level of risk can be further reduced by using low-dose aspirin treatment.
Pignone	2006	USA	men 45 y. 10-years risk 7.5% or higher:	Aspirin vs. no aspirin: dominant	Probalistic sensitivity analyses: men 45 y. 10-years risk 7.5% or higher: 91% cost-saving One-way sensitivity analyses: excess risk for hemorrhagic stroke and gastrointestinal bleeding with aspirin, risk for CHD, the cost of statins, and the disutility of taking medication had important effects on the cost-utility ratios	Compared with no treatment aspirin is less costly and more effective for preventing CHD events in middle-aged men whose 10-year risk for CHD is 7.5% or higher.

Tsutani	2007	Japan	men and women 1-years risk of CHD of 1,5% or more	Aspirin vs. no aspirin; dominant	The aspirin arm was dominant to no aspirin arm, regardless of the cost of stroke. Sensitivity analyses on GI bleeding rate, stroke rate, cost of each event and discounting showed the robustness of the results	Aspirin therapy should be recommended in the primary prevention of CVD in all individuals who have at least a moderately increased risk of CHD and who do not have an increased risk of GI bleeding events.
Pignone	2007	USA	65 year old women,7.5 % 10-year risk of CHD, 2.8% risk of stroke	Aspirin vs. no aspirin: €12,103 per QALY	Age, CVD-risk, RR reductions with aspirin for ischaemic stroke and MI, excess risk of hemorrhagic stroke and GI and disutility of taking medication.	Firm conclusions about the aspirin effect are limited by the imprecision of available evidence. Aspirin is indicated for women at higher risk for stroke, but should not be prescribed for low-risk women, including most younger women.

Exercise programme to prevent falls and fall-related injuries in independently living elderly

First Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Beard	2006	Ausralia	Men and women >60years	Fall prevention program vs. no program: BCR Perspective: 1. commonwealth government: 13.75:1 2. Australian community: 20.6:1		These findings suggest that well-designed community-based interventions targeting fall prevention among older people are highly cost-effective and a wise investment for all levels of government
Robertson	2001	New Zealand	men and women >80 years	Exercise program vs. no program; €1,200 fall prevented	results are robust	
Robertson	2001	New Zealand	women >80years	Exercise program vs. no program Fall prevented: €248 Injury prevented: €361	Results are robust to changes in costs	
Rizzo	1996	USA	Men and women >70 years	Intervention vs. no intervention: dominant per fall prevented and injury prevented	It appears that the cost-effectiveness of the intervention is insensitive to alternative assumption regarding intervention cost	

N-3 Polyunsaturated Fatty Acids (PUFA) as tertiary prevention after myocardial infarction

First Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Franzosi	2001	Italy	Patients with recent (<3 months) MI	PUFA vs. no PUFA: €31,984 per LYS	analysis of extremes: best and worst scenario best: ICER 20,437 worst: ICER 68,281	The cost-effectiveness ratio of long term treatment with n-3 PUFA appears comparable with other preventive drugs recently introduced in routine secondary prevention after MI.
Schmier	2006	USA	Men with acute MI	PUFA vs. no PUFA MI avoided: Year 1: €15,630 3.5 year: €9,326 CV death avoided, including productivity costs: dominating	MI avoided: sensitive for supplementation costs and the effects of supplementation on MI rates. CV death avoided: robust	Despite model limitations omega-3 supplementation should be considered an important and cost-effective option for prevention of secondary cardiovascular events.
Quilici	2006	UK	Patients with recent MI	4-years QALY: €22,480 Lifetime QALY: €5,510 4-years LYS: €17,776 Lifetime LYS: €4,162	did not change the base case results substantially	The use of Omacor® as a standard post-MI prevention treatment seems warranted both on basis of the efficacy of the product, as evidenced by the results of the GISSI-P trial, and the cost-effectiveness ratios, both at 4 years and over a lifetime horizon.
Lamotte	2006	Australia Belgium	Patients with recent (<3	Belgium: 42 months: €5,300 per	1. lifelong 2.cost of complications 3.varying discount rate 4.varying cost of Omacor®: Lifelong: except	Administering highly concentrated n-3 PUFAs may be cost effective for the secondary prevention of

	Canada, Germa-ny Poland	months) MI	LYS; lifetime €9,410 per LYS	Poland the ICER doubled. All other case small differences in the ICER.	cardiovascular disease after MI in the five countries studied.
			Germany: 42 months € 4,372 LYS; lifetime €8,648 per LYS	Assuming the country specific willingness to pay threshold: Cost-effectiv in Poland 93%, in other countries 98%	

Lifestyle intervention to prevent diabetes mellitus

First Author	Year	Country	Target group	Cost-effectiveness	Sensitivity	Remarks
Diabetes Prevention Program Research Group	2003	USA	IGT	Lifestyle intervention vs. placebo: €15,812 diabetes prevented	The findings for the lifestyle intervention were most sensitive to the format of the intervention.	
Herman	2005	USA	IGT	Lifestyle intervention vs. placebo: €1,135 per QALY Metformin vs. placebo: €31,598 per QALY	>50years: ICER €4,178	
Palmer	2004	Australia France Germa-ny Switzer-land and UK	IGT	Intensive lifestyle changes vs. control dominating (except UK; €6,870)	when the effects of the interventions on the incidence of DM were varied between the bounds of the reported 95%CIs both ILC and metformin remained life saving with all values within the 95% CIs	
Caro	2004	Canada	IGT	Lifestyle vs. no treatment €577 per LYS Lifestyle vs. metformin €5,585 per LYS	Under most scenarios, both metformin and lifestyle modification either led to savings or were highly cost-effective in comparison with no treatment	
Jacobs-van der Bruggen	2007	Holland	IGT	Lifestyle vs. no intervention; community and healthcare: € 3,939	costs of intervention were varied and the discout rates to. All ICERs remain <€ 20000	
Icks	2007	Germa-	IGT	Lifestyle	patient participation en intervention effect	

	ny	intervention vs. no intervention: €4,851

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