Vaccination HPV pour la prévention du cancer du col de l'utérus en Belgique: Health Technology Assessment

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Federaal Kenniscentrum voor de Gezondheidszorg
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PREFACE

La vaccination de l'ensemble des femmes (et pourquoi pas aussi des hommes) contre les infections liées au HPV annonce la fin du cancer du col de l'utérus! C'est ainsi que les médias populaires nous présentent les choses. Voilà un an en effet qu'un premier vaccin contre le HPV est disponible sur le marché. Il sera bientôt remboursé en Belgique pour les jeunes filles de 12 à 15 ans et un deuxième vaccin vient de s'ajouter au 1ier octobre 2007.

Mais en quoi consiste ce vaccin réellement et quel serait le résultat d'une vaccination massive des jeunes filles sur l'incidence du cancer du col de l'utérus ? Quel serait l'impact sur le dépistage actuel ? Pourrait-il être arrêté ou faudrait-il le maintenir ? En quoi la vaccination influencerait-elle la perception du risque du cancer du col de l'utérus chez les femmes vaccinées et en quoi influerait-elle négativement le dépistage ? Finalement, quel en serait le coût pour l'assurance maladie et la société ?

Ce rapport d'évaluation des technologies de la santé (Health Technology Assessment - HTA) tente de répondre à certaines de ces questions. Les preuves disponibles de l'efficacité et de la sécurité du vaccin ont été synthétisées et combinées avec les données disponibles quant aux bénéfices et coûts attendus. De même un certain nombre de zones d'ombre, généralement passées sous silence, sont traitées dans ce rapport, e.g. la durée de protection du vaccin, la nécessité d'un vaccin de rappel et la fréquence de ce vaccin de rappel.

Nous sommes bien conscients que ce rapport n'apporte pas de réponse définitive à toutes les questions posées. Cependant, la prise de décision en milieu incertain fait partie intégrante de la médecine et de la politique des soins de santé.

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RÉSUMÉ

INTRODUCTION

Au niveau mondial, le cancer du col de l'utérus est le deuxième cancer le plus répandu chez les femmes (après le cancer du sein), avec 500.000 nouveaux cas chaque année selon les estimations. Il s'agit de l'une des rares formes de cancer pour laquelle un virus a pu être identifié comme étant la cause, le papillomavirus humain (HPV). L'infection et le cancer qui en résulte pourraient dès lors en théorie être prévenus au moyen d'un vaccin contre le HPV.

L'infection par HPV est une infection commune et omniprésente qui se transmet par voie sexuelle. Sur les quelque 100 génotypes de HPV actuellement identifiés, plus de 40 peuvent infecter les voies génitales, et ceux-ci ont été classés en génotypes (à haut et faible risque) indiquant leur niveau d'association avec le cancer du col de l'utérus. Parmi les génotypes à haut risque fréquemment détectés, épinglons le HPV type 16, détecté dans près de la moitié des cancers du col de l'utérus, et le HPV type 18, souvent détecté dans les formes glandulaires du cancer du col de l'utérus. Une infection persistante avec l'un des types de HPV à haut risque oncogénique est une condition nécessaire, mais pas suffisante, pour développer un cancer du col de l'utérus de nombreuses années plus tard.

La majeure partie des femmes (et des hommes) sera infectée à un moment ou l'autre de leur vie sexuelle active, par le HPV et viendra spontanément à bout de l'infection. La prévalence la plus élevée de l'infection par HPV est constatée chez les femmes de moins de 25 ans, avec ensuite un déclin soutenu de la prévalence du HPV au fur et à mesure qu'elles prennent de l'âge (au moins aux USA et en Europe du Nord). Une infection persistante avec un génotype de HPV à haut risque est nécessaire au développement de lésions précancéreuses (lésions CIN) et, finalement, d'un cancer du col de l'utérus invasif après des années voire des décennies. Il s'est avéré efficace de faire subir aux patientes un test de dépistage des lésions intermédiaires (et de les traiter si nécessaire) sur la base des cellules obtenues à la surface du col de l'utérus. Dans les pays appliquant le dépistage cytologique (test PAP) tous les 3 à 5 ans chez les femmes âgées de 25 à 65 ans, jusqu'à 80 % des cas invasifs du cancer du col de l'utérus peuvent être évités. En Belgique, où un programme de dépistage organisé fait défaut mais où il y a un degré élevé de dépistage opportuniste, le cancer du col de l'utérus n'est qu'à la 10^{e} place des cancers les plus fréquents chez les femmes, représentant chaque année près de 600 cas, soit 2,8 % de l'ensemble des cas de cancer.

Deux vaccins concurrents contre le HPV, Gardasil et Cervarix, ont été développés. Gardasil est disponible depuis 2006 et contient des antigènes basés sur deux génotypes de HPV à haut risque (16 et 18), et deux autres types de HPV (à faible risque), 6 et 11, pertinents pour la prévention des condylomes génitaux associés au HPV. Cervarix, disponible depuis peu sur le marché belge contient uniquement des antigènes basés sur les génotypes de HPV 16 et 18.

Ces deux vaccins empêchent avec succès l'infection par le type de HPV contenu dans le vaccin. Toutefois, l'importance relative des réponses immunitaires cellulaires et humorales dans la protection contre l'infection au HPV après la vaccination n'est pas très bien connue et un marqueur de protection facile à mesurer n'a toujours pas pu être défini. Étant donné que c'est la première fois qu'un vaccin a le potentiel de vente d'un médicament à très grand succès, un effort de marketing sans précédent a été déployé par les fabricants.

Dans la presse non spécialisée, 'la fin du cancer du col de l'utérus est annoncée et le vaccin aurait prétendument 100 % d'efficacité dans la prévention de l'infection par les *'pires formes de HPV'*. Dans le présent rapport d'évaluation de technologie de santé (HTA), nous nous efforçons de présenter une vision équilibrée des avantages potentiels pouvant découler de la vaccination, mais aussi des dangers potentiels sur la base de ce que nous connaissons aujourd'hui. Nous fournissons un aperçu de la littérature

économique relative à la vaccination contre le HPV et avons mené une évaluation économique de l'introduction potentielle d'un programme de vaccination en Belgique.

Dans près de 70% des cancers du col de l'utérus, les HPV types 16 et/ou 18 peuvent être détectés. Ce pourcentage est souvent présenté comme étant la proportion minimale de cancers du col de d'utérus qui sera éliminée après l'introduction du vaccin. Toutefois, avec les techniques de détection plus récentes, il est devenu apparent que dans plusieurs cancers contenant le HPV16 / 18, d'autres génotypes de HPV à haut risque peuvent être présents. Dans ces cas, l'attribution des lésions à un génotype unique n'est pas possible et même une élimination totale du type 16 / 18 peut ne pas être suffisante pour éviter le cancer. En d'autres termes, la proportion de cancer du col de l'utérus contenant uniquement le type 16 / 18 comme type à haut risque pourrait ne pas dépasser les 60 %, comme le fait apparaître une récente étude de population.

Exception faite du cancer du col de l'utérus, quelques autres types de cancers plus rares sont également attribués au HPV : les cancers génitaux provenant de la vulve, du vagin et du pénis ainsi que les cancers de l'anus, du canal anal et certains cancers de l'oropharynx. Les données relatives à l'efficacité des vaccins HPV dans la prévention de ces cancers sont limitées. C'est la raison pour laquelle ces cancers n'ont pas été inclus dans notre modèle économique du vaccin contre le HPV.

EFFICACITE ET SECURITE DU VACCIN CONTRE LE HPV

Gardasil est commercialisé sur le marché américain et européen depuis 2006. Cervarix a été approuvé par l'EMEA en juillet 2007 et est disponible sur le marché belge depuis le 1ier octobre 2007. Les preuves disponibles sont principalement fondées sur le Gardasil ; pour le Cervarix, seules des preuves limitées sont publiquement disponibles.

Gardasil

Dans des essais cliniques randomisés, menés sur des femmes de 16 à 26 ans *non précédemment infectées* par des HPV à haut risque ('HPV naïve' – plusieurs définitions sont utilisées), Gardasil a démontré sa capacité à réduire de 99 % (95 % CI 93-100) le taux de dysplasie de haut degré liée au HPV 16 ou 18 (CIN 2+) *et de 46 % (24-62) le taux de dysplasie cervicale de haut degré en général*. Il réduit également le taux de dysplasie vulvaire et vaginale de haut degré de 81 % (51 – 94).

Chez les femmes qui étaient infectées par des souches de virus HPV contenues dans le vaccin, aucune preuve de l'efficacité du vaccin n'a pu être apportée. Sur tous les sujets enrôlés dans les essais cliniques randomisés du Gardasil, 27 % étaient positives pour au moins l'un des 4 types de vaccins HPV au début de l'étude, et 21 % pour le HPV 16 et / ou 18. Dans ce groupe mixte, l'efficacité du Gardasil dans la prévention des lésions CIN 2+, indépendamment du type de HPV, était de 18 %, ce qui reflète le mélange de jeunes femmes susceptibles et non susceptibles dans cette population.

Les essais sur le Gardasil n'ont pas été menés dans le groupe cible, à savoir les filles de 12 ans. Toutefois, des 'études d'extrapolation' ('bridging studies') ont indiqué que la réponse immunitaire humorale observée chez les jeunes filles (et garçons) n'était pas inférieure à la réponse immunitaire humorale chez les jeunes femmes adultes.

La *durée de la protection est inconnue*. Les études actuelles couvrent des périodes pouvant atteindre 5 ans et un suivi sur le plus long terme sera nécessaire pour déterminer si et quand un vaccin de rappel serait approprié. Dans l'évaluation économique, nous avons utilisé plusieurs scénarios et l'analyse de sensibilité probabiliste pour traiter cette incertitude. Nous ne connaissons pas non plus les effets à long terme du vaccin sur l'épidémiologie de l'infection par HPV, nous ignorons si un remplacement de souche peut causer des lésions précancéreuses par exemple, ou si, dans les infections mixtes actuelles incluant à la fois les souches inclues dans le vaccin et d'autres souches, les autres souches sont tout aussi oncogènes.

Aucun de ces deux vaccins ne pose actuellement un problème de sécurité. Bien sûr, les données de sécurité issues des essais cliniques randomisés sont par nature limitées, et le nombre d'effets secondaires est réduit. De plus, la sécurité a principalement été étudiée

sur les populations d'essai, composées de jeunes femmes adultes de 16 à 26 ans, et non sur le groupe cible de jeunes filles. Toutefois, des études post-commercialisation de grande envergure sont actuellement en cours comme demandé par la FDA et l'EMEA, pour évaluer ces problèmes de sécurité au sein de grandes populations du groupe cible.

Cervarix

Les données publiquement disponibles sur l'efficacité et la sécurité du Cervarix sont encore *insuffisantes pour pouvoir tirer des conclusions définitives*, car seuls des essais cliniques randomisés de phase II ou des analyses intermédiaires d'études de phase III ont été publiées, et les données soumises aux autorités chargées d'autoriser la mise sur le marché n'ont pas été mises à notre disposition.

Les données préliminaires font apparaître une efficacité de vaccin sur les lésions CIN 2+ liées aux souches du vaccin semblable à celle du Gardasil. On n'a pas mesuré l'effet sur les condylomes génitaux étant donné que les souches de HPV 6 et 11 ne sont pas incluses dans ce vaccin. Toutefois, le suivi est court et nous n'avons pas pu retrouver des données relatives à l'efficacité du vaccin pour la réduction de l'ensemble des lésions CIN2+, indépendamment de la souche de HPV impliquée (exception faite de données d'essai de phase II).

ÉVALUATION ECONOMIQUE ET MODELE POUR LA BELGIQUE

Dans la littérature, de nombreux modèles se sont efforcés d'évaluer le profil économique du vaccin contre le HPV. Tous ces modèles, y compris celui que nous avons développé nous-mêmes, posent un problème majeur : le manque de données pour la quantification d'hypothèses cruciales. Certains modèles sont qualifiés de 'statiques', suivant une cohorte de femmes vaccinées, tandis que d'autres sont appelés 'dynamiques', et tiennent compte de la transmission du virus entre les individus. Ces derniers modèles sont, en théorie, supérieurs aux modèles statiques, car ils permettent l'inclusion de ce que l'on appelle les *'effets d'immunité de groupe'*. Dans la pratique, toutefois, ces modèles doivent se fonder sur un nombre encore plus élevé d'hypothèses et d'incertitudes que les modèles statiques.

En Belgique, seul 59% des femmes participent au moins une fois tous les trois ans au dépistage du cancer du col de l'utérus. En considérant les cas de cancers du col de l'utérus observés, ainsi que le nombre de cas attendus sans screening, nous avons calculé que le dépistage touche dans les faits environ 80% des femmes appartenant au groupe d'âge cible.

La plupart des modèles publiés concluent que la vaccination contre le HPV des jeunes filles de 12 ans pourrait s'avérer coût efficace comparé aux pratiques actuelles en matière de dépistage. Aux USA, les *Incremental Cost Effectiveness Ratios* (ICER) calculés vont de €22 200 à €23 300 par '*Quality Adjusted Life Year Gained*' (QALY) dans les modèles statiques. Les ICER dans les modèles dynamiques sont moins élevés et vont de €2 600 à €14 200 par QALY gagnée. La seule étude européenne ayant fait état du coût par QALY provient de Norvège ; cette étude a mis en lumière un ICER de €39 400 par QALY gagnée. Une étude danoise a uniquement rapporté le coût par année de vie gagnée (€8 700).

En présence de grandes incertitudes, tout modèle économique doit se fonder sur des hypothèses. Toutefois, un défaut majeur de la plupart des études préalablement publiées est qu'elles se fondent en grande partie sur des hypothèses sans toutefois se livrer à une analyse de sensibilité probabiliste. En raison des importantes incertitudes entourant les hypothèses cruciales, nous avons décidé de développer notre propre modèle, basé sur des données belges, dans le but premier d'évaluer l'influence relative des différentes incertitudes sur les estimations des ICER. Les hypothèses les plus importantes que nous avons souhaité analyser étaient l'impact du taux de participation au dépistage après vaccination, le taux d'actualisation pour les coûts et les effets et les incertitudes entourant la durée de protection du vaccin.

Nous avons développé un modèle statique de Markov au moyen d'une tables de survie multi états (*'Multi State Life Table'*). Nous avons opté pour une conception simple, afin

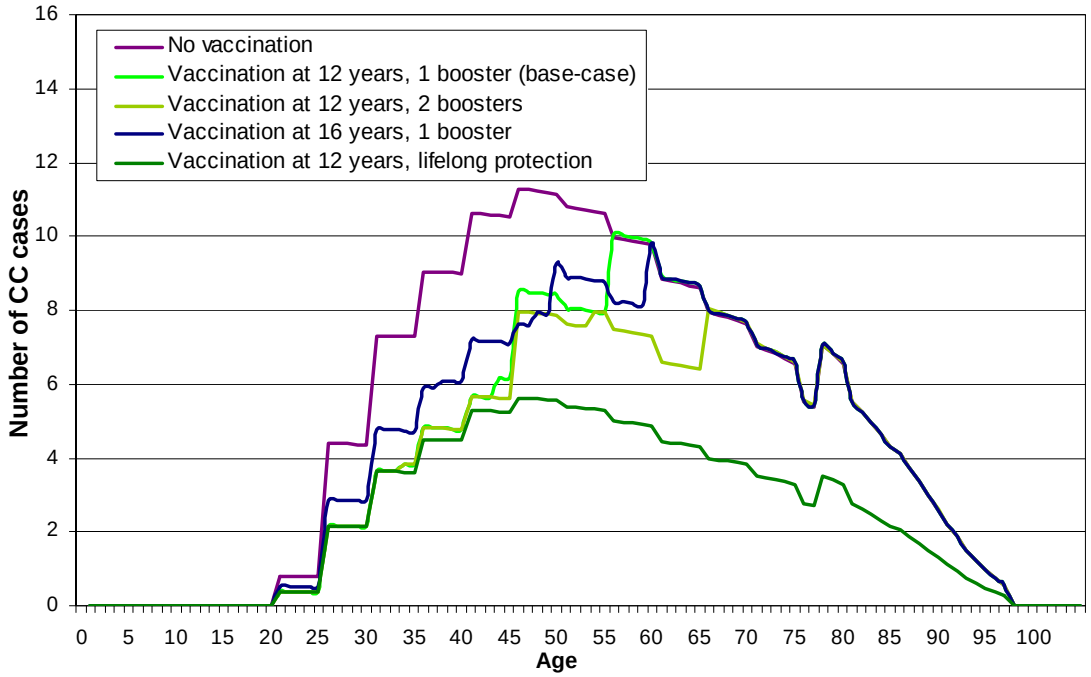
d'éviter au maximum les transitions pour lesquelles peu de données fiables n'étaient disponibles. L'une des décisions majeures fut d'éviter de modéliser la progression clinique des états *'infection – lésions précancéreuse – cancer du col de l'utérus'*, mais de modéliser directement les lésions précancéreuses (pour évaluer les coûts et les résultats du dépistage) et les cancers du col de l'utérus.

Le modèle a spécifiquement trait à la vaccination dans le cadre d'un programme public organisé et non à la vaccination opportuniste. Pour cette raison, nous nous sommes basés sur un coût moins élevé que le prix *ex-officine* et avons supposé une couverture élevée tant pour le vaccin d'origine que, dans certains scénarios, pour le vaccin de rappel.

En supposant une baisse de la protection du vaccin au fil du temps, une vaccination de rappel après 10 ans et des taux d'actualisation de 3 % pour les coûts et de 1,5 % pour les effets, un programme de vaccination contre le HPV en Belgique coûterait près de €33 000 par QALY gagné, par comparaison avec le screening seul, avec un large intervalle de confiance (95%) de quelque €17 000 à €68 000. Environ 20% des cas de cancers du col seraient évités par la vaccination dans ce scénario. En supposant une immunité à vie, le coût par QALY gagnée tomberait à près de €14 000. Comparé aux modèles publiés, le nôtre prévoit des rapports coût efficacité plus élevés si, à l'instar de ce qui se fait dans la plupart des modèles dans la littérature, tant les coûts que les effets étaient actualisés à 3 %. Dans ce scénario le ICER dans notre modèle est environ €56 000 par QALY.

L'impact de la vaccination en Belgique est illustré dans le graphique ci-dessous. La vaccination contre le HPV entraîne une réduction du nombre absolu de cancers du col de l'utérus variant de 20% pour le scénario de base (une vaccination de rappel) jusqu'à 50% en supposant une immunité à vie.

Nombre de cas de cancers du col de l'utérus par année et par âge, pour différents scénarios de vaccination.



Conserver le taux de couverture du dépistage à des niveaux élevés devrait constituer une priorité essentielle, étant donné que la majeure partie pour ne pas dire tous les bénéfices de la vaccination seraient perdus en cas de diminution légère de la couverture du dépistage. Si les jeunes filles étaient toutes vaccinées, le dépistage n'en resterait pas moins un outil essentiel dans la lutte contre le cancer du col de l'utérus. Pour les jeunes

femmes non dépistées et non vaccinées, le risque à vie pour le cancer du col dans notre modèle serait de 1 sur 28. Le vaccin sans dépistage et une protection à vie ramèneraient ce chiffre à 1 sur 70. Un dépistage adéquat sans vaccination toutefois, ramènerait ce chiffre à 1 sur 217, alors que l'ajout de la vaccination au dépistage le ramènerait à 1 sur 556. Dans le scénario de base, nous avons trouvé qu'une réduction de la couverture effective du dépistage de près de 10 % anéantirait tous les effets de la vaccination de cohortes entières de jeunes femmes.

Au terme d'une période de stabilisation, la vaccination contre le HPV représenterait un investissement net annuel de €24 millions pour le budget de la santé. Cet investissement doit cependant être examiné à la lumière des dépenses actuelles en rapport avec le dépistage opportuniste du cancer du col, puisque ces dépenses sont sensiblement plus élevées que dans un scénario de dépistage optimal qui serait basé sur les recommandations. En théorie, un programme de vaccination contre le HPV pourrait être largement financé sur le même budget, si les coûts de dépistage étaient mieux contrôlés et mieux ciblés.

Enfin, il convient de souligner que d'importantes zones d'ombre subsistent, tant au niveau de l'efficacité du vaccin qu'au niveau de la durée de protection. Ces zones d'ombre ne peuvent pas être éclairées sur la base des preuves actuelles. Qui plus est, de grandes incertitudes subsistent au sujet de l'histoire naturelle du cancer du col de l'utérus.

PROBLEMES ETHIQUES ET ORGANISATIONNELS

Lorsqu'on considère la vaccination massive de jeunes filles saines, le principe éthique de *'ne pas nuire'* devrait être examiné avec un soin particulier. En raison des incertitudes liées au vaccin contre le HPV, l'image trop optimiste véhiculée par les médias quant aux bénéfices du vaccin devrait être contrebalancée par des informations indépendantes, correctes et complètes pour permettre un choix éclairé par les décideurs et les individus.

Une vaccination universelle mise en œuvre au travers d'un programme officiel peut permettre une meilleure couverture, en particulier pour les groupes socialement défavorisés. Elle peut également assurer un coût moins élevé pour le vaccin au travers de l'achat de vaccins en grosses quantités.

Des analyses économiques, comme nous en avons mené dans notre modèle, peuvent nous aider à mieux comprendre l'impact des incertitudes dans les données, mais elles sont également limitées dans leur potentiel à définir des seuils, par exemple, pour des âges spécifiques pour lesquels un programme de rattrapage unique serait envisageable. Pour ce genre de décisions, il faudra considérer les incertitudes sur l'efficacité et le rapport coût efficacité, l'impact budgétaire et la faisabilité opérationnelle d'un tel programme de rattrapage.

L'introduction combinée d'un registre de vaccination et de dépistage, couplé au registre du cancer, pourrait contribuer au maintien ou à l'amélioration de la couverture de dépistage et pourrait permettre de surveiller l'efficacité et la sécurité d'un programme de vaccination contre le HPV.

CONCLUSIONS ET RECOMMANDATIONS

- Les vaccins actuels contre le HPV sont seulement efficaces dans la prévention de l'infection par les génotypes HPV couverts par le vaccin et des lésions cervicales précancéreuses liées à ces génotypes, chez les femmes non encore infectées par ces génotypes. Chez ces femmes, 46% des lésions précancéreuses causées par tout génotypes HPV sont évités.
- Les vaccins actuels ne sont pas efficaces contre un de ces génotypes HPV spécifiques chez les femmes ayant précédemment été infectées par ces génotypes.
- Même si les jeunes filles étaient toutes vaccinées contre une infection par le HPV dès leur plus jeune âge, le dépistage demeurera un outil essentiel dans la lutte contre le cancer du col de l'utérus. Pour les jeunes filles qui ne sont pas dépistées et non vaccinées, le risque à vie de cancer du col dans notre modèle serait de 1 sur 28. La vaccination sans dépistage et avec une protection à vie ramènerait ce risque à 1 sur 70. Un dépistage adéquat sans vaccination, toutefois, ramènerait ce chiffre à 1 sur 217, alors que l'ajout de la vaccination au dépistage le ramènerait à 1 sur 556 dans notre modèle de protection à vie du vaccin.
- Le modèle économique se réfère uniquement à un programme de vaccination publiquement organisé. Le modèle a été alimenté avec les données d'efficacité issues des essais sur le Gardasil uniquement, étant donné que des données pertinentes pour le Cervarix n'étaient pas disponibles. Pour peu que l'efficacité du Cervarix à réduire le nombre global de lésions CIN2+ chez les femmes naïves au HPV soit comparable au Gardasil, le modèle s'appliquerait également au Cervarix, étant donné qu'aucune hypothèse n'a été formulée sur les résultats en rapport avec des cancers autres que le cancer du col de l'utérus.
- Maintenir la couverture du dépistage à des niveaux élevés devrait être une priorité majeure, même en cas de mise en œuvre de la vaccination contre le HPV. Parallèlement à un programme de vaccination, l'introduction d'un registre pour le dépistage couplé au registre du cancer pourrait constituer un outil permettant d'accroître la participation à la vaccination et au dépistage.
- Une partie du coût du programme de vaccination contre le HPV pourrait être récupérée si le programme actuel de dépistage du cancer du col de l'utérus était mieux organisée.
- La durée de la protection de la vaccination est largement méconnue étant donné que, actuellement, le suivi est limité à 5 ans. Une vaccination de rappel pour les deux vaccins sera-t-elle nécessaire ou pas? La question reste ouverte.
- En raison des incertitudes liées à la vaccination contre le HPV, l'image trop optimiste véhiculée par les medias devrait être contrebalancée par des informations indépendantes, correctes et complètes pour permettre un choix éclairé par les décideurs et les individus.

SCIENTIFIC SUMMARY

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AGC	Atypical Glandular Cells
AIS	Adenomacarcinoma In Situ
ASC-H	Atypical squamous cells: cannot exclude a high-grade squamous intra-epithelial lesion
ASC-US	Atypical Squamous Cell of Undetermined Significance
BLA	Biologic License Application (FDA)
CC	Cervical Cancer
CCTR	Cochrane Controlled Trial Register
CDC	Centers for Disease Control and Prevention
CEA	Cost Effectiveness Analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIN	Cervical Intra-Epithelial Neoplasia
CIN I	CIN: Mild cell changes
CIN 2	CIN: Moderate cell changes
CIN 2+	Histological lesions CIN 2 and above (CIN 2, CIN 3, SCC)
CIN 3	CIN: Most severe cell changes
CIS	Carcinoma In Situ
CTG - CRM	Commissie Terugbetaling Geneesmiddelen - Commission Remboursement des Médicaments
DNA	DeoxyriboNucleic Acid
EGL	External genital Lesions
EMEA	European Medicines Agency (EU)
EU	European Union
FDA	Food and Drug Administration (USA)
FU	Follow-up
GMT	Geometric Mean Titre
HC2	Hybrid Capture II
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
IARC	International Agency for Research on Cancer (WHO organisation)
ICC	Invasive Cervical Cancer
ICER	Incremental Cost Effectiveness Ratio
IR	Incidence Rate
ITT	Intention-To-Treat (population)
IVD	In Vitro Diagnostics
LA	Linear Array (HPV detection test)
LBC	Liquid Based Cytology
LE	Life Expectancy
LEEP	Loop Electrosurgical Excision Procedure
LiPA	Line Probe Assay (HPV detection test)
LLETZ	Large Loop Excision of the Transformation Zone

LSIL	Low-grade Squamous Intraepithelial Lesion
LYG	Life Year Gained
MITT	Modified Intention to Treat (RCT population)
MMR	Mumps – Measles – Rubella vaccination
MSLT	Multi State Life Table
NOS	Not Otherwise Specified
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PP	Per-protocol (population)
PP	Private Practitioner
PY	Person Years
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
RIZIV-INAMI	National Institute for Health and Disability Insurance
RMITT	Restricted Modified Intention to Treat (RCT population)
RR	Relative Risk
RRP	Recurrent Respiratory Papillomatosis
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SCJ	Squamocolumnar Junction
SIR	Susceptible – Infected - Recovered
SIS	Susceptible – Infected - Susceptible
STI	Sexually Transmitted Infection
TBS	The Bethesda System
TGA	Therapeutic Goods Administration (Australia)
USA	United States of America
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine Efficacy
VIA	Visual Inspection with Acetic acid
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus Like Particle
WHO	World Health Organisation

1 INTRODUCTION

1.1 CERVICAL CANCER AND HPV VACCINATION

In women, cervical cancer is the second most common cancer worldwide, with an estimated 500 000 new cases and 250 000 deaths in the year 2005.[1] Almost 80% of cases occur in developing countries where cervical cancer can account for up to 15% of incident cancers in women.[2] In most developed countries, however, cervical cancer incidence is much lower nowadays, mainly due to more or less well organised screening, either opportunistic screening such as in Belgium or through screening programs as in many Northern-European countries. In Belgium, cervical cancer incidence is only at the 10th place of most common cancers in women, accounting for about 2.8% of cancers.[3] The Belgian Cancer Registry,[4] reports for Belgium an absolute number of 588, 601 and 595 incident cervical cancers for the years 2001, 2002 and 2003 respectively. It should be noted, however, that those numbers might be slightly underestimated because in the data for the Brussels and Walloon regions of the country their might still be some underreporting.[4]

The link of cervical cancer with sexual activity was suggested long ago when it was reported that cervical cancer rarely occurs amongst nuns.[5] Since the beginning of the nineteen nineties, and the use of PCR techniques, it has been demonstrated that virtually all cervical cancer cases can be shown to be associated with a genital infection with a single or multiple oncogenic strains of the Human Papillomavirus (HPV),[2] a very common viral sexually transmitted infection (STI). There are 40 different genotypes of HPV than can infect the ano-genital area in both men and women. Strongest epidemiological evidence for association with cervical cancer is available for HPV types 16 and 18 that are the most frequent genotypes associated with cervical cancer, but at least 13 HPV types are considered high-risk oncogenic.[6] Some of the other HPV genotypes are considered low-risk types and are associated with condyloma accuminata, especially types 6 and 11. The lifetime risk for infection with HPV is very high, but cervical cancer occurs in only a small minority of women; this difference is due to the fact that most HPV infections are cleared spontaneously while only persistent infections will ultimately lead to precancerous lesions that, if remaining undetected through screening, can evolve into invasive cervical cancer.

Until recently, regular screening was the only way to prevent cervical cancer, and in Belgium screening every three years between the ages of 25 and 64 is recommended, but in practice the situation is one of over screening (often yearly) in a subgroup of the target population of about 60% while there is no screening or irregular screening in another part of the target population.[7]

In recent years, however, promising vaccines have been developed that aim at preventing HPV infections. One vaccine (Cervarix®) targets HPV types 16 and 18, while another (Gardasil®) targets the same two HPV types but additionally targets types 6 and 11, aiming at also preventing condyloma accuminata. These vaccines appear to be very effective in preventing infection and precancerous cervical lesions caused by these HPV specific strains but there are major concerns about their effectiveness on a population level. Although they effectively target the most frequent HPV types associated with cervical cancer, there is no solid evidence that there is an effect on other oncogenic strains. For this reason, current screening can not be scaled down at this moment, although it is expected that in the future new vaccines that effectively target a wider range of HPV strains will become available. Another reason for concern is that it is uncertain how long the protective effect will last; current data are limited to about 5 years of follow-up, while most economic evaluations to date assume a lifelong protection, sometimes with a booster after 10 years.

To help address these concerns and to evaluate the uncertainties we conducted this Health Technology Assessment of current preventive HPV vaccines.

1.2 REGULATORY STATUS OF CURRENT VACCINES

1.2.1 Gardasil®

Gardasil® is a quadrivalent HPV vaccine (HPV 6/11/16/18) produced by Merck and marketed in Europe by Sanofi-Pasteur-MSD. In the European Union, the CHMP issued a positive opinion for granting a Marketing Authorisation to Gardasil® on 27 July 2006 and the European Commission adopted the corresponding decisions on 20 September 2006.[8] In the US, the Biologic Licence Application (BLA) was approved by the FDA on July 8th, 2006 for sale and marketing to girls and women ages nine to 26, after a Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC) on May 18th, 2006.[9, 10] The CDC's Advisory Committee on Immunization Practices (ACIP) later that month voted unanimously to recommend that girls aged 11 and 12 receive the vaccine.[11]

In Belgium, Gardasil® is on the market, currently only partly reimbursed by some of the Sickfunds. It was recently evaluated by the Commission for Reimbursement of Pharmaceutical Products (CTG – CRM) for possible reimbursement through the federal social security and in September 2007, Gardasil® received a positive opinion for reimbursement for the vaccination of girls aged 12 to 15 years of age. Previously the Belgian superior health council had recommended the yearly vaccination of a cohort of young females between the ages 10 and 13 years with this HPV vaccine.[12]

In many other European countries the situation is similar as in Belgium, with in several countries recommendations from health authorities to vaccinate cohorts of females before sexual initiation but with varying states of reimbursement of the vaccine.

1.2.2 Cervarix®

Cervarix® is a bivalent HPV vaccine (HPV 16/18) produced by GSK. Until recently, it was not on the market in Europe. GSK announced on April 3rd that it filed for FDA approval of Cervarix® in the US. At this moment it is unknown whether and when marketing application will be granted in the US. The Cervarix® application, however, has been approved in Australia,[13] and in July 2007 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending to grant a marketing authorisation for Cervarix® intended for prophylaxis against high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18.[14] Following this EMEA approval,[15] Cervarix® has become available on the Belgian market since October 1st, 2007.

2 EPIDEMIOLOGY OF HPV INFECTION AND HPV-RELATED BURDEN OF DISEASE

HPV infection is a common, omnipresent sexually transmitted infection. Over 100 HPV types have been established; over 40 infect the genital tract. They have been classified into high-risk, and low-risk genotypes (see table in the appendix for this chapter). Infection with one of the high-risk, oncogenic HPV types is a necessary, but not a sufficient cause for cervical cancer. HPV has also been causally related to some other cancers in the ano-genital region and in the oropharynx in men and women. Most women will at some time of their life be infected with HPV but few will progress to invasive disease.

2.1 HPV INFECTION

2.1.1 Incidence and prevalence of HPV infection

Most women are infected with HPV shortly after sexual debut. A study in the UK using longitudinal data from women who had only one sexual partner until that moment, found that the risk of acquiring cervical HPV infection was 46% (95% CI 28-64) at three years after first intercourse and that the median time from first intercourse to first detection of HPV was only three months.[16]

The highest prevalence of HPV infection is seen in women under 25 years, with a steady decline in HPV prevalence observed with increasing age, at least in the United States and Northern Europe. There are wide variations between countries, however, and in some countries a second but smaller peak is observed after the age of 40. In a representative sample of women in the Netherlands (a country expected to be comparable to Belgium in that respect) HPV prevalence was 15.4% among 15-24 year old, and 2.8% among women over age 55.[17]

2.1.2 Incident versus persistent infection

Most HPV infections are transient and clear spontaneously, and it is accepted that a persistent infection with a high-risk HPV is necessary for the development of high grade CIN. However, the definition and measurement of a 'persistent infection' face profound methodological challenges.[18] It is not possible to determine how long a women has been infected when she tests positive in her first sample. It also remains to be determined whether persistent infections are characterized by the continuing detection of HPV, or by a state of latency during which the virus remains undetectable, only to reappear later.[18]

This has important implications. A woman cannot be labelled as having a persistent infection only because she tests positive for the same HPV type on 2 different occasions. Therefore she should not be considered to have a higher risk of cervical cancer only based on two consecutive positive tests. Alternatively, a woman who tests positive for a specific HPV type can not be assumed to have cleared the infection when she first tests negative for that type. A clearer understanding of these issues is essential for the effective implementation of screening strategies which might include HPV testing.[18] Despite these methodological challenges, however, it is expected that in the future the concept of persistent infection, i.e. the same HPV genotype detected at more than 2 occasions over a timeframe of 12 months, will be considered as an indicator for the evaluation of vaccine efficacy.

2.1.3 HPV viral load and disease

The relationship between viral load and disease is more complex than was previously assumed. It varies with the infecting HPV type, the physical state of the virus (integrated in the host cell genome or not, and the method used to determine it) and the heterogeneity of cervical lesions.[18]

The prevalence of integrated forms of HPV increases with disease severity, and integration itself is followed by a decrease in viral load; HPV 16 viral load seems associated with increasing disease severity whereas HPV 18 is not, and cytological changes observed after HPV 18 infection might underestimate the severity of the underlying histological abnormality.[18] This might obviously have important implications for screening and referral procedures based on the detection of cytological abnormalities. The complexity of these relationships also indicates that a measurement of viral load does not appear to be clinically useful.

2.1.4 Multiple infections

The concurrent or sequential detection of more than one HPV type is common.[18] In a survey of more than 15 000 women without apparent cervical abnormalities, out of 955 women infected with at least one high-risk HPV type, 346 (36%) had multiple infections.[19] In a cervical screening population in the UK, 40% and 42% of mild and high-grade cervical lesions respectively, were found to harbour multiple high-risk HPV infections.[20]

There is some evidence to indicate that the life cycles of different HPV types are not independent of each other, as had previously been assumed. For example in women with HSIL, HPV 16 viral load is higher when other HPV types are present than when HPV 16 is present alone.[18] It is still not clear whether infection with multiple HPV types interferes, either directly or immunologically, with the persistence of a given HPV type or with progression.[21] In addition, the assay limitations need to be taken into account as described below.

2.1.5 Limitations of the genotyping assays and their implications

The promise of genotype 16/18 preventive vaccines is largely based on their high type specific efficacy and the observation that HPV genotype 16 and/or 18 can be detected in about 70% of the cervical cancer samples. As in the original publication,[22] only in a few percentages of samples other high risk genotypes were detected together with type 16 or 18, little attention was given to mixed high risk infections. Probably due to improved assay sensitivity a higher proportion of high risk mixed infections in cervical cancer lesions was reported more recently. Correspondingly, the proportion of 'pure' 16/18 cervical cancers decreased to only 60% using a sensitive genotyping technique.[23] The relevance of this observation for prediction of population efficacy is self explanatory. The attribution of HPV lesions to a given genotype is tricky in case of mixed HPV infections. In case of a mixed infection of genotype 16 with another high-risk type, the lesion has, in epidemiological studies, typically been attributed to genotype 16, and not to e.g. genotype 52 when also present in the mixture. Another attribution algorithm, in conflict with the above mentioned rule, was used in reporting type specific efficacy of a 16/18 vaccine, where sequential results were available.[24]

Accurate tests for HPV genotyping are thus required for epidemiologic studies of HPV infections by specific genotype, and to assess the efficacy of type-specific vaccines. Genotyping methods have evolved over time. Currently there exists no reference test method for HPV genotyping. Some of the available HPV genotyping tests are now CE labelled, but none has passed the FDA IVD hurdle yet.[25] Genotyping tests used in endpoint definitions of confirmatory clinical trials are mainly custom-made, and need to be validated.

What are the challenges for genotyping? In contrast to serum based tests for viral nucleic acids, the source material for HPV genotyping is a cervical smear (often LBC) or cervical biopsy material, which makes it more difficult to standardise sample collection and testing.

The quantities of HPV DNA present in the sample collected may vary with sampling technique, with the grade of cervical lesions, the genotype of the virus, as well as with host factors. Most HPV typing assays used in epidemiologic studies are based on 'consensus PCR' to amplify the relatively conserved L1 gene region with hybridization (reverse blot assays eg Line Probe Assay, LiPA, Innogenetics, or Linear Array, LA, Roche), restriction enzyme digestion, or sequencing of the amplicon to determine type(s). Widely used L1 consensus primer PCR systems include the GP5+/6+,[26, 27] My09/11,[28] SPF10 systems,[29] or combinations thereof.

In general, the HPV typing methods used in epidemiological studies are hampered by variations in the efficiency of type-specific priming, primer competition, and limitations on the reagent concentrations in the assay.[30] This may lead to variations in the observed type distribution, particularly when multiple types at greatly different copy numbers are present before and/or after amplification. This is illustrated by the large variation in frequency of mixed infections reported in studies of invasive cancer and high-grade cervical lesions.[31] Interpretation of the few studies comparing HPV genotyping methods is hampered by the lack of a reference standard. The MY09/11 primer set was less sensitive compared with the SPF10 primer set,[32] and type-specific PCRs.[33] A comparison of the SPF10-based INNO-LiPA with the Roche linear assay showed an agreement in types detected for 129 of the 160 samples (80.6%).[34]

There is a potential detection bias in HPV genotyping in case of mixed infections containing HPV genotype 16, because of a relatively higher viral load of type 16, especially in more advanced lesions compared with other types.[35] It might well be that genotype 16 only is detected because the other high-risk types present do not represent the minimal proportion (1-5%?) of the total amplified material, required for detection using LiPA or LA tests. Despite the limitation of these methods, in about half of the type 16/18 infections other high-risk HPV types were detected in high-grade lesions (K S Cushieri, personal communication) and 12 to 22% of mixed HPV infections were found in cervical cancer specimens.[36] Using multiplexed PCR assays for 12 high risk types[37] mixed high-risk infections were detected in about 30% of CIN 2/3 and about 15% of the cancer lesions. [23] Perhaps more relevant for predicting theoretical efficacy of a genotype 16/18 vaccine, the population-based study in Iceland showed that 40% of the 441 CIN 2/3 samples and 60% of the 141 cervical cancer samples contained only genotype 16 and/or 18.[23]

In conclusion, awaiting further standardisation of HPV genotyping methods, results based on not fully validated tests should be interpreted with caution.

2.1.6 Immune response to HPV infection

Most studies support the notion that humoral responses to naturally occurring infections exert little protective effect against HPV persistence or HPV-related disease. Recurrence of the same type is uncommon suggesting that humoral response do give some protection. However, one should be aware that the HPV epitopes responsible for the cellular or humoral immune response after infection or vaccination do not necessarily vary by HPV genotype and may thus induce cross-protection. On the other hand the immune response may in theory be limited to an epitope which is not conserved within a given genotype and thus induce only partial protection to all variants of a given genotype. There is relatively good clinical evidence that cell-mediated immune response is critical for viral clearance after infection is established.[21] In a large proportion of women who have detectable HPV infection measurable antibodies against specific HPV types are never detected.[21]

Animal model data suggest a protective role for vaccine-induced antibodies.[38] The relative importance of the cellular and humoral immune response after HPV vaccination is poorly documented. Based on the relatively low seroconversion rate for type 18 Merck vaccine (68%),[39] and a higher protection rate against type 18 specific infection one could deduct that the cellular immune response must be the most relevant correlate of protection, but this has not been documented further.

2.2 CERVICAL CANCER

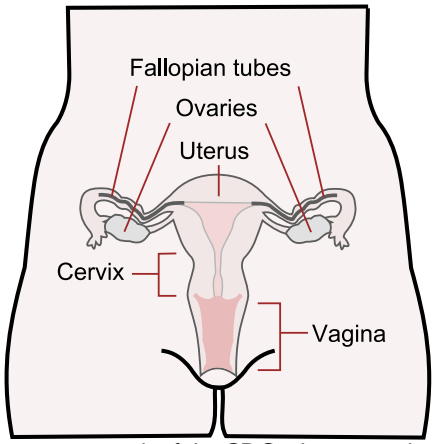
2.2.1 Incidence, risk factors, histology, and survival

Cancer of the cervix uteri is the second most common cancer among women worldwide and 80% of cases occur in developing countries.[2] Virtually all cervical cancers can be associated with HPV infection, leading to an inference of causality. In Western-Europe and North-America age-standardized incidence rates are now below 15/100 000.[2] These data are obviously influenced by the fact that basically all Western countries either have a cervical cancer screening programme or have, as in Belgium, widely applied opportunistic screening. In Belgium, for example, cervical cancer only comes at the 10th place of incident cancers in women.[3]

Worldwide, the general form of the curve of incidence versus age shows a rapid rise to a peak usually in the 5th or 6th decade (ages 40 to 60), followed by a plateau and a variable decline.[2] This pattern reflects the natural history of infections with HPV and the related carcinogenic mechanisms. This typical age profile might be distorted by screening (as shown for example by the Belgian data further in this chapter), and also by the use of cross sectional data rather than longitudinal data if there should be important birth-cohort effects on cervical cancer risk.[2]

Cervical cancer originates from the cells in the lower part of the neck (cervix) of the uterus. The female anatomy is illustrated in figure 1.

Figure 1: Illustration of female anatomy frontal view including cervix uteri.



Studies have been consistent in finding associations between risk of cervical cancer and early age at initiation of sexual activity, increasing number of sexual partners (either the females themselves or their partners), and other indicators of sexual behaviour.[2] It is likely that different observed associations of classical demographic variables with risk of cervical cancer are largely the result of differences in exposure and possibly response to HPV, as well as to differences in patterns of screening.

Women of lower socio-economic status have a higher risk for cervical cancer incidence and mortality. This has been observed before the era of screening for instance in the United Kingdom, 1949-1953.[40] In addition they are also less likely to be screened.[41]

The majority of cases of cervical cancer are squamous cell carcinomas (SCC); adenocarcinomas are less common. In general, the proportion of adenocarcinomas cases is higher in areas with a low incidence of cervical cancer, and this histology may account for up to 25% of cervical cancers cases in many Western countries.[2, 42] The relatively high proportion of adenocarcinomas in highly developed countries is mainly attributed to the screening which, at least in the past, had probably little effect on reducing the risk of adenocarcinoma of the cervix because these cancers, and their

precursors, occur within the cervical canal from the glandular epithelium and were not readily sampled by scraping the epithelium of the ectocervix using the Pap test.[42]

Worldwide survival rates of invasive cervical cancer vary according to stage at diagnosis as shown for a few countries in table 1.

Table 1: Five-year relative survival (%), by stage, in the USA, Finland and India

	Stage		
	Local	Regional	Distant
USA (white) 1992-99	93	52	17
Finland, 1985-94	84	49	28
Mumbai India, 1982-86	77	35	6

Relative survival takes into account deaths from other causes.
Adapted from IARC handbook of cancer prevention [2] page 8

2.2.2 HPV genotypes in cervical lesions and attribution of causality

Virtually all cases of cervical cancer are attributed to HPV infection. The most frequently detected HPV types at the time of diagnosis of cervical cancer are HPV 16, and HPV 18. HPV 18 is more often associated to adenocarcinoma. The best data in that respect come from a pooled analysis combining data from an international survey of HPV types in cervical cancer and a multi-centre case-control study (see table in appendix).[22]

A theoretical calculation based on these data, taking into account the estimated region-specific HPV genotype distribution and number of cases of incident cancers, led to the widely quoted estimation that 'HPV 16 and HPV 18 are responsible for 71% of cervical cancers worldwide'.[22]

However these figures should be interpreted with caution. These data were collected from 1985 to 2000 and the technique and performance of genotyping testing have strongly evolved over time. As test's sensitivity might depend on viral load, as we discussed earlier in this chapter, these data might underestimate the prevalence of genotypes for which viral load is usually lower, for instance HPV 18, and that of mixed infections. The fact that the lifecycle of different HPV types is not independent of each other,[18] conceptually challenges the very idea of a linear attribution of causality to one genotype when multiple infections are present and calls for caution when anticipating the population impact of an HPV vaccine based on the assumed prevalence of the vaccine genotypes in cervical cancer.

HPV distribution in high-grade cervical lesions is not entirely representative of that in invasive cervical cancer (ICC). A meta-analysis identified an overrepresentation of HPV 16, 18 and 45 in ICC as compared to HSIL (prevalence ratio: 1.3, 1.76, and 1.76 respectively).[31]

2.2.3 Steps in cervical carcinogenesis

Pre-malignant changes represent a spectrum of histological abnormalities ranging from CIN 1 (cervical intraepithelial neoplasia grade 1, or mild dysplasia) to CIN 2 (moderate dysplasia) to CIN 3 (severe dysplasia and carcinoma in-situ). However this is not, as was once believed, one of progression of CIN 1 to CIN 2 to CIN 3 and eventually to invasive cancer. Cytological and histological examinations cannot reliably distinguish the few women with abnormal smears who will progress to invasive cancer from the majority of those with abnormalities who will spontaneously regress. Based on data derived from a Dutch population-based screening program, the interval between the manifestation of the earliest lesion (CIN 1) and the development of cervical cancer was estimated at about 12.7 years.[43, 44]

CIN 1 indicates the presence of active HPV infection and is not considered pre-cancerous. The preferred management option for CIN 1 is expectant management without treatment as at least 70% of these lesions will regress spontaneously and there will be plenty of time to detect and treat the other 30% while still benign.[45]

There is substantial heterogeneity in microscopic diagnosis and biological meaning of **CIN 2** lesions. Some certainly represent acute HPV infections of particularly bad microscopic appearance, destined to regress, while others are incipient pre-cancers and are destined to persist with high grade invasion. Some non carcinogenic HPV infections are capable of producing lesions diagnosed as CIN 2, thereby showing that this level of abnormality is not sufficient for cancer risk.[21]

CIN 3 is a good indicator of subsequent cancer risk. CIN 3 lesions tend not to regress over short term follow-up; however the risk and timing of invasion vs. eventual regression is probabilistic. The median age of women with CIN 3 lesions is 27-30 years while the median age of women with invasive cervical cancers is shifted too much older ages, which suggest a long sojourn time in precancerous CIN-3 states.[21]

The above mentioned sojourn times are poorly documented and the distribution unknown. One also needs to distinguish between invasive cervical cancer detected after screening and symptomatic cases. Therefore caution is needed when adding above mentioned durations.

Table 2 presents an overview of the classification systems used to classify and name precancerous conditions of the cervix, based on either cytology or on histology.

Table 2: Cervical precancerous lesions: different terminologies used for cytological and histological reporting

Cytological classification (used for screening)		Histological classification (used for diagnosis)	
Pap	**Bethesda system**	**CIN**	**WHO descriptive classifications**
Class I	Normal	Normal	Normal
Class II	ASC-US ASC-H	Atypia	Atypia
Class III	LSIL	CIN 1 including flat condyloma	Koilocytosis – Mild dysplasia*
Class III	HSIL	CIN 2	Moderate dysplasia
Class III	HSIL	CIN 3	Severe dysplasia
Class IV	HSIL	CIN 3	Carcinoma in situ
Class V	Invasive carcinoma	Carcinoma	Invasive carcinoma

CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells: cannot exclude a high-grade squamous epithelial lesion.
Source: Adapted from WHO, Comprehensive Cervical Cancer Control.[1]
* Personal Communication Patricia Claeys, 14 September 2007.

2.2.4 The rationale for screening

It has been calculated that screening *all* women between 25 and 64 years every 3 years has the potential to reduce by 90% the cumulative incidence of invasive cervical cancer as compared to no screening.[7]. However coverage in European countries is not complete and was found to vary from 27% in Spain to 93% in Finland (data from before 2000).[46] Improving coverage of cervical screening programmes is a major public health issue. Recommendations for screening interval (3 to 5 years) and age group vary slightly between countries.[47, 7]

When high-grade lesions are suspected through cytology (either the classical Pap smear or liquid based cytology) the standard practice for diagnosis are colposcopy and a biopsy for subsequent histopathological assessment, if suspicious lesions are detected during the colposcopy.

2.2.5 Clinical management

Cervical intraepithelial neoplasia and micro invasive cervical cancer detected through screening and subsequent diagnosis are treated with procedures such as cryotherapy, cold knife conisation, laser conisation, loop electrosurgical excision procedure (LEEP) also called large loop excision of the transformation zone (LLETZ). In a meta-analysis all these excisional procedures presented similar pregnancy-related outcomes.[48] For instance LLETZ was significantly associated with preterm delivery (RR 1.70, 95% CI 1.24–2.35) corresponding to 11% vs. 7%, low birth weight (1.82, 1.09–3.06) and premature rupture of the membranes (2.69, 1.62–4.46).[48] Occasionally, hysterectomy is performed for the indication of cervical dysplasia, depending on specific patient conditions and preferences. The clinical management of invasive cervical cancer consists of surgery or radiotherapy, with or without chemotherapy.[1]

2.3 OTHER CANCERS RELATED TO HPV

A few other cancers have also been linked to HPV infection: cancers of the vulva and the vagina in women, of the penis in men, and cancers of anus, mouth and oropharynx in both genders.

Age-standardized incidence rates of cancers of the vulva in most countries lie between 0.5 and 1.5/100 000 women. Cancer of the vagina is less frequent. It is estimated that 40% of the cancers of the vulva, and the vagina, are attributable to HPV infection and of these 40%, 80% might be due to HPV 16 or 18.[42] For cancers of anus and anal canal, it is estimated that around 40 and 65% is attributable to HPV in men and women respectively.[42] Although HPV infection is accepted as an etiological factor for oral and pharyngeal cancers, the major risks factors for these are tobacco and alcohol.[42]

2.4 NON CANCEROUS HPV-RELATED OUTCOMES

HPV 6 and 11 are low-risk HPV types and are the causal agents for ano-genital warts (condylomas) and recurrent respiratory papillomatosis (RRP). In the UK, lifetime reported prevalence of ano-genital warts was 3.6% for men and 4.1% of women aged 16 to 44 years.[49] RRP is a rare condition characterized by recurrent growth of benign papillomas in the respiratory tract. The papillomas are benign but their recurrent nature and location require frequent surgical removal. Annual incidence is 3.5/10 million in Denmark.[49]

2.5 CERVICAL AND OTHER HPV-RELATED CANCER INCIDENCE IN BELGIUM

Most recent incidence data available from the Belgian Cancer Registry are for 2003. Every year around 600 cases of invasive cervical cancer are diagnosed in this country, [4] putting cervical cancer on the 10th place of cancer incidence in women.[3] In addition to these 600 cases of invasive cervical cancer, 131 vulvar, 36 vaginal and 78 cancers of anus or anal canal were diagnosed in Belgian females in 2003.

Table 3: Selected cancers in females, Belgium, 2003

	N	Crude	1 year age-standardized* incidence/100 000	Cumulative risk (0-74 ys)
Cervix uteri	595	11.2	9.8	0.8
Vulva	131	2.5	1.6	0.1
Vagina	36	0.7	0.5	0.0
Anus/anal canal	78	1.5	1.1	0.1

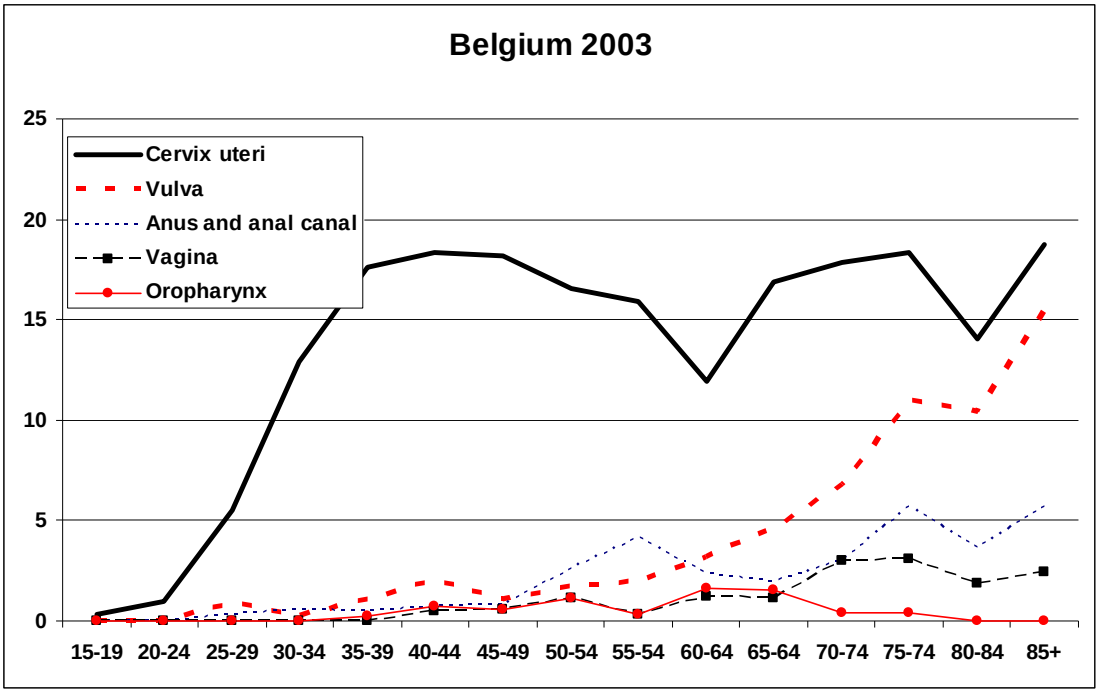
*Age-standardised for European Reference Population.
Source: Cancer data: Belgian Cancer Registry Foundation.[4]

Standardized incidence rates for these cancers are broadly similar across the 3 regions (Flemish, Walloon and, Brussels regions: see tables in appendix for more details).

Distribution of cancer incidence by age in Belgium in 2003 is shown in figure 2. Cervical cancer incidence increases with age up to a plateau that is reached at age 35-39. After

the age of 50 incidence decreases slightly and is lowest at ages 60-64. After that age the cervical cancer incidence rises again. Similar patterns are found in the years 2001 and 2002. Of the other cancers that are linked to HPV, only the incidence of vulvar cancer increases markedly with age.

Figure 2: Selected cancers in females, by age at diagnosis. Belgium 2003.



Source: Cancer data: Belgian Cancer Registry Foundation.[4]

In table 3 we applied the estimated HPV-attributable fraction to the Belgian cancer incidence data to estimate the total cancer burden associated with HPV in this country.

Table 4: Cancers associated with HPV infection in Belgium, 2003

Site	N	associated with HPV (%)	of which, associated with HPV 16/18 (%)	N associated with HPV 16/18
Females				
Vulva	131	40%	80%	42
Vagina	36	40%	80%	12
Cervix uteri	595	100%	70%	417
Oropharynx	21	12%	89%	2
Anus and anal canal	78	90%	92%	65
Males				
Anus and anal canal	48	90%	92%	40
Penis	50	40%	63%	13
Oropharynx	75	12%	89%	8

Source: Cancer data: Belgian Cancer Registry Foundation.[4]
HPV attributable fractions: Parkin.[42]

From these data it would appear that 22% of the cancers attributable to HPV 16/18 in females are non cervical cancers. However these are only very rough estimates and caution should be used before equating 'associated with HPV 16/18' with 'preventable by an HPV vaccine targeting genotypes 16/18' (see previous discussion on causality). Also, given the age distribution of these cancers the benefits to be expected from a vaccine targeting genotypes 16 and 18 given to teenage girls could be observed, in the best case scenario, only beyond 30 to 40 years after start of the vaccination programme.

2.6 CERVICAL CANCER SURVIVAL IN BELGIUM

The observed 5-year survival from invasive cervical cancer in Flanders was 65.2% in 2000-2001, while the relative 5-year survival was 68.4%. The data for 1, 3 and 5 year survival are shown in table 4.[3]

Table 5: HPV infection-attributable cancers in Belgium, 2003

	Relative survival			Observed survival			Cancer	Death
	1 year	3 year	5 year	1 year	3 year	5 year	N	N
Cervical Cancer	87.8	73.9	68.4	86.8	71.7	65.2	1 854	1 508

Source: Flemish Cancer Registry 2000-2001.[3]

2.7 CERVICAL CANCER SCREENING IN BELGIUM

In Belgium screening is currently recommended every 3 years from 25 to 64 years.[7] Data on coverage of the Belgian female population for cervical cancer screening are mainly derived from an analysis of individual social security reimbursement data from 1996 to 2000.[50] Coverage, when defined as the proportion of women within the target group that had at least one cytological examination (Pap or LBC) in the last 3 years, was 59% in 2000. If this definition was changed to include a 5 year interval (such as for example recommended in the Netherlands), coverage was 67%.[50, 7] Moreover, it should be remembered that those proportions include all women, including women who had previously undergone a total hysterectomy, and that also women undergoing irregular cytological examinations benefit from some protection. In the economic model in chapter 5 we therefore used the concept of 'screening coverage equivalent' derived from the difference in observed and expected cervical cancers with and without screening. For Belgium, we calculated that this screening coverage equivalent is around 79% in women who have not undergone total hysterectomy.

Screening coverage also varied by age, increasing to a maximum of 67% (3-year interval definition) in women of 30-34 years then decreasing to 56% of in the 50-54 years old group, and after that coverage declined more rapidly. We did not find data on socioeconomic inequalities regarding screening participation in Belgium.

While not enough women were screened in Belgium between the ages of 25 to 64, those that were screened had a cytological examination too frequently. Moreover, 17% of cytological examinations were taken outside the target range (10% under 25 years, 7% age 65 and over). The modal screening interval in the database was one year. Each screened women received on average 1.88 cytological examinations over a 3 year-period. Taking into account examinations done for follow-up of abnormal results, this study estimated every year 600 000 cytological examinations taken in Belgium did not contribute to screening coverage or follow-up. A ratio of one colposcopic examination for every 3 cytological examinations and a very low biopsy/colposcopy ratio (5%) indicated that colposcopy was often performed in perfectly normal women and not, as recommended in national or international guidelines, in case of cytological abnormalities.

There were 5 088 and 7 007 cervical excision procedures performed in 2000 and 2005, respectively.[7] Overall, it is estimated that around 1 400 cases of invasive cervical cancer are prevented each year through those current (sub-optimal) screening activities.[7]

Key points

- **HPV infection is a common, omnipresent sexually transmitted infection. Some oncogenic HPV types are causally related to cervical cancer in women and to some other cancers in the ano-genital region and in the oropharynx in men and women.**
- **Most women will at some time of their life be infected with HPV but few will progress to invasive disease.**
- **The highest prevalence of HPV infection is seen in women under 25 years of age, with a steady decline in HPV prevalence with increasing age, at least in the US and in Northern Europe.**
- **Most HPV infections are transient and clear spontaneously, and it is accepted that a persistent infection with a high-risk HPV is necessary for the development of high grade CIN. However, the definition and measurement of a 'persistent infection' face profound methodological challenges. Despite these challenges, it is expected that this concept will become even more important for the future evaluation of new HPV vaccines.**
- **Most studies support the notion that humoral responses to naturally occurring infections exert little protective effect against HPV persistence or HPV-related disease and the relative importance of the cellular and humoral immune response and protection after HPV vaccination is poorly documented.**
- **As HPV 16/18 infections mixed with other high-risk genotypes are nowadays detected more frequently, the attribution of lesions to a single genotype may not always be possible.**

3 EFFICACY AND SAFETY OF PREVENTIVE HPV VACCINATION

Existing HPV vaccines target the most frequent HPV types 16 and 18, which have been found on average in 50% and 20% of cases of cervical cancers respectively (with some minor geographical variations).[22] These vaccines have shown almost 100% efficacy in preventing infections with HPV 16 and 18 types up to 5 years (for Gardasil) after vaccination,[51] leading to the assumption that such a vaccine could potentially prevent around 70 % of cancers worldwide.

A variety of plausible but yet unproven mechanisms such as cross-protection (against strains not included in the vaccine), strain replacement or strain interaction (whereby infection by a given HPV type may affect the risk of infection and/or disease with another HPV type) might challenge this simple extrapolation and drive vaccine efficacy above or below the prevention of 70% of cervical cancers, even given a 100% efficacy in preventing type-specific infection. For instance several studies have found that infection with HPV 6 and 11 reduces the likelihood of developing cervical cancer in those also infected with HPV 16. The elimination of HPV 6 and 11 might therefore increase the oncogenic potential of certain infections.[52] From a public health point of view it also makes sense to assess the efficacy of the vaccine on all lesions, not only on strain-specific ones. On the other hand, genotype 16/18 infections may also contain other high-risk genotypes.

The objective of this chapter is to review the existing evidence on the overall efficacy of HPV vaccines on cervical cancer and on its precursors regardless of the specific HPV strain associated with it, rather than on HPV infections.

3.1 CURRENT PREVENTIVE HPV VACCINES

This chapter will review the prophylactic efficacy and safety of the two HPV vaccines that are either currently on the market. Table 6 gives an overview of the main characteristics of current HPV vaccines.

Table 6: Comparison of main characteristics of current Quadrivalent and Bivalent vaccines

	Quadrivalent (6/11/16/18)	Bivalent (16/18)
Name	Gardasil (Merck/Sanofi Pasteur MSD)	Cervarix (GSK)
Type	Recombinant – type specific HPV virus-like particle (VLP)	
HPV 6	20 µg	-
HPV 11	40 µg	-
HPV 16	40 µg	20 µg
HPV 18	20 µg	20 µg
Adjuvant	225 microg aluminum (hydroxyphosphate sulphate)	500 microg alum plus 50 microg 3-O-desacyl-4'-monophosphoryl lipid A (AS04)
Licensed	FDA: June 2006: EMEA: September 2006	Marketing application submitted to EMEA/FDA. March 2007, approved in Australia, EMEA positive opinion approved July 2007.
Cost in Belgium	€137.4 /dose *3= €412	€137.4 /dose *3= €412*

Antigens and adjuvants used for these vaccines are different, but no data are available to compare their respective immunogenicity.
*Cervarix is available on the Belgian market since October 1st, 2007.

3.2 ENDPOINTS AND INDICATORS CONSIDERED FOR EFFICACY

Endpoints available from RCTs are either HPV type-specific i.e. related to the HPV types included in the vaccine being evaluated, or not type-specific i.e. regardless of HPV type. For reasons discussed earlier this distinction is crucial for the evaluation of overall protection against cervical cancer

3.2.1 Immunogenicity and seroconversion

Geometric mean titre (GMT): the measurement of anti-HPV antibody titers is specific to the HPV type and the laboratory assay used. Numeric values of specific titres cannot be compared between HPV types or across trials using different methods. It is not known whether these antibodies are protective and the threshold for seroconversion is arbitrary. GMTs are used (1) to compare natural and vaccine humoral immunity (within a particular trial) (2) to study the duration of the humoral immune response and (3) to compare vaccine-induced humoral immunity between groups, in particular between adolescent girls and women. Young girls represent the population most likely to benefit from the vaccine as they have not yet been exposed to HPV infections. On the other hand efficacy studies cannot be conducted in sexually naïve girls as these are not yet at risk for HPV infection.[53] Therefore these studies would take too much time to conduct before results could be observed. To overcome this lack of evidence in adolescents, 'bridging studies' are conducted: if it can be shown that adolescents show an immune response to the vaccine similar to that observed in adult women, then it is assumed that efficacy results observed in adult women can be 'bridged' to adolescent girls who form the core target group for the vaccine. To our knowledge no bridging study data have been made public for cellular immune response tests.

3.2.2 Cervix related endpoints

HPV vaccines are intended to prevent cervical cancer. However as the standard of care involves removing or excising its precursors, cervical cancer is not a feasible endpoint for these clinical trials. Another reason is that malignancies develop slowly and cancer as an endpoint requires very large and lengthy studies.[54] Therefore histological abnormalities, after biopsy of suspect cervical lesions, are used as endpoints in RCTs. Those histological endpoints are categorized according to degree of dysplasia. More details on the classification of these histological and cytological abnormalities can be found in the previous chapter.

3.2.2.1 Histology

Histological diagnoses of cervical abnormalities are reported as cervical intraepithelial neoplasia (CIN 1, 2 and 3), adenocarcinoma in situ (AIS), or cancer. CIN 2, CIN 3, AIS and cervical cancer are collectively referred to as 'CIN 2+'.[55]

Cancer precursors include CIN 3, AIS, and to a lesser extend CIN 2. The likelihood of progression to cancer is higher, and the time to progression shorter, as the grade of dysplasia increases. CIN 2 is not an irrefutable cancer surrogate since up to 40% lesions regress spontaneously. [53] Histological differentiation between CIN 2 and CIN 3 is not sufficiently reliable however to permit a clear stratification of risk and as a consequence immediate treatment of CIN 2 and CIN 3 lesions with excision or ablation is recommended for non-pregnant patients (although watchful expectant management is recommended for adolescents).[55]

Although a surrogate for cervical cancer, **CIN 2+** (CIN 2/3 and above) histological abnormalities were accepted by the American Food and Drug Administration as the preferable primary endpoint for clinical trials assessing the efficacy of HPV vaccines against cervical cancer[56]. CIN 2+ might not be a perfect predictor of cancer risk, but they represent the current indication for treatment.

3.2.2.2 Cytology

Cytological abnormalities (Pap or LBC): following the revised Bethesda system, these are classified into Atypical Squamous Cell of Undetermined Significance (ASC-US), Low-grade Squamous Intra-epithelial Lesion (LSIL), and High Grade Squamous Intra-epithelial Lesion (HSIL).

3.2.2.3 HPV infection

HPV infection is a necessary but not sufficient condition for cervical cancer.

Incident infection is defined in RCTs as at least one positive PCR result. Most HPV infections are silent and transient and of little clinical significance. As PCR assays are extremely sensitive, they will detect very small amount of HPV-DNA possibly as a result of HPV presence not related to active infection or very low-grade transient infection.

Persistent cervical HPV infection: persistent infection is believed to be necessary to develop Cervical Intraepithelial Neoplasia (CIN), although sensitivity and specificity of different duration thresholds as predictors for evolution towards cancer are unknown. It is defined in RCTs as 2 positive HPV-DNA PCR assays for the same viral genotype separated by a given time period, often 6 or 12 months. This definition, however, does not allow to differentiate between persistent and multiple transient infections. 'Persistent infection' rates cannot be compared across trials if the time period used to define them is not similar. For these reasons, the use of HPV infections as an endpoint for clinical trials of HPV vaccines is sometimes challenged.[57]

3.2.3 Vulval and vaginal endpoints

Vulvar Intraepithelial Neoplasia (VIN 2 and 3) and Vaginal Intraepithelial Neoplasia (VaIN 2 and 3) are precursors of cancer.[58]

3.2.4 Condylomas

Condylomas (warts) are relevant endpoints for the quadrivalent vaccine, since these are caused by the additional virus types (HPV 6 and 11) included in this vaccine.

3.2.5 Vaccine efficacy and population impact

The vaccine efficacy (VE) is the proportion of events (endpoints) prevented by the vaccine in the vaccinated group. It is computed as (1 – rate ratio) x 100. (rate ratio: rate of events in vaccine group/rate of events in placebo group).

The VE can be expressed as HPV-specific vaccine efficacy i.e. the efficacy against endpoints associated with a specific vaccine genotype. This is applicable in case there is only a single HPV genotype involved. In case of mixed infections the situation is more complex and multiple possibilities exist for attribution of vaccine HPV-specific efficacy, as discussed previously.

It can also be expressed as VE against endpoints associated with specific other HPV types (other than those included in the vaccine) as a measure of possible cross-protection offered by the vaccine. At the contrary, it might be used as a measure of possible replacement of genotypes when a decrease in HPV vaccine specific endpoints is being offset by an increase in non-vaccine-specific HPV endpoints.

Finally, VE can be expressed against endpoints regardless of HPV type, which is also called the population impact, or overall impact. It is the proportion of all clinical events prevented by the vaccine regardless of HPV type. This is the most relevant measure for public health purposes.

3.3 OBJECTIVES AND RESEARCH QUESTIONS

Although HPV infections are a necessary, but not sufficient condition for cervical cancer, we did not consider infection endpoints specifically for the following reasons:

- incident HPV infections are of little direct clinical importance
- there are serious problems involved in defining and measuring persistent infections in clinical trials
- histological endpoints were identified by the FDA as the preferable endpoints for the evaluation of efficacy of HPV vaccines.

Therefore we have decided to focus the review of efficacy on histological endpoints because of their clinical significance: CIN 2/3 or worse (CIN 2+), VIN and VaIN 2/3 or worse, and condylomas.

Our research questions are:

- What is the efficacy (and duration of protection) of current HPV vaccines:
  - in the prevention of CIN 2+ precancerous lesions, both HPV-specific and regardless of HPV type?
  - in the prevention of vulvar and vaginal cancers, and in the prevention of condylomas, both HPV-specific and regardless of HPV type?
- How are efficacy data observed in women 18-23 years old translated ('*bridged*') to younger females (or boys) for current HPV vaccines?
- What is the safety/tolerability of current HPV vaccines?

3.4 METHODS

3.4.1 Search for primary data: efficacy and safety of HPV vaccines

On March 30th, 2007 we searched Medline, Embase, and the Cochrane Controlled Trials Register (CCTR) for data published since 2000. Detailed search algorithms are described in the appendix. An update search was conducted on June 3rd, 2007.

In addition to data published in the scientific literature, we searched the websites of the American (FDA) and European (EMEA) drug regulatory authorities for the technical documents prepared by these bodies to support the licensing procedure. These documents are supposed to be *independent* reviews of the 'complete study report' required from the manufacturer when filing for approval of a particular product. This report contains all data available to the manufacturer at the time of submission, including unpublished data. As a matter of principle we preferably did not consider manufacturer's documents available on these websites but not independently reviewed (for example slide shows), although we sometimes refer to these data when they provide some added value or when it is the only possible reference for important data.

- For the objective 1 (efficacy) our inclusion criteria were randomized controlled trials (RCTs) phase 2 or 3, reporting on histological abnormalities CIN 2+, VIN 2-3, VaIn 2-3 or condylomas.
- For objective 2 ('bridging' efficacy) our inclusion criteria were studies comparing immune response in older women to immune response in younger girls (and boys).
- For objective 3 (safety) we considered data from RCTs phase 2 or 3 or post-marketing pharmacovigilance data, if available.

3.4.2 Search results

Our search obtained 243, 159, and 24 hits in Medline, Embase and the CCTR, respectively. All but 10 were sifted out on the basis of the title and abstract (main reasons for exclusion: not an RCT or phase I RCT); 8 could contribute to at least one of our objectives. The update search identified 5 additional articles, including 2 combined analysis of data from RCTs published earlier (see details in appendix).

For Gardasil we retrieved the technical documents prepared by EMEA,[8] and FDA,[9] respectively. These documents contain data from all trials, but also present pooled results from several trials. On the FDA website we also found slide shows and minutes of the meeting that led to the approval of Gardasil licensing in June 2006.[56, 59] Cervarix has only recently obtained marketing approval in the EU, but not in the US and we found no formal FDA, EMEA or TGA (Australia) documents detailing the results from the trials. In October 2007, while finalising this report, the EPAR for Cervarix became publicly available.[15] However, it contained no surprises and it did not provide details on the impact of Cervarix on all CIN 2+ lesions regardless of HPV-genotype

For both products some information in the form of slide shows and transcripts of the US Advisory Committee on Immunization Practices (ACIP) meetings are available at the ACIP website.[60]

3.5 PRIMARY DATA AVAILABLE FOR ASSESSMENT

3.5.1 Quadrivalent vaccine – Gardasil (HPV 6/11/16/18)

The efficacy of the quadrivalent vaccine has been assessed in 4 placebo-controlled, double blind, randomized phase II and III trials, so-called protocols 005,007,013, and 015. All are industry-funded (see table 7). Protocol 005 (phase II trial) only evaluated the HPV 16 component of Gardasil.[61, 62] Protocol 007 was a dose-ranging phase II trial designed to select one of three formulations of quadrivalent HPV (types 6/11/16/18) for use in phase III studies.[37] Protocols 013 (FUTURE I)[63] and 015 (FUTURE II)[39] are phase III trials with results published in May 2007. These are all multi-centre studies with comparable methods in terms of selection of participants and procedures including definition of endpoints and outcome measurement, allowing pooling of the results.[9] Combined analyses of those RCTs have recently been published for vulvar and vaginal endpoints (protocols 007, 013 and 015),[58] and for cervical endpoints.[64] A description can be found in table 2.

EMEA[8] and FDA[9] technical documents report more detailed and pooled data from these studies, including population efficacy data that are left unreported in the publications.

CIN 2+ lesions to assess the efficacy of HPV vaccines are rare events when follup-up period is limited as in current trials. We therefore focus on the combined analyses when available, and present data from individual trials only when they have added value as compared to combined data.

Table 7: RCTs of Gardasil vaccine efficacy

	Protocol 005	**Protocol 007**	**Protocol 013 FUTURE I**	**Protocol 015 FUTURE II**
Type	Phase II – proof of concept	Phase II – dose-ranging	Phase III	Phase III
Intervention	40 µgr HPV 16 L1 VLP	Quadrivalent HPV 6/11/16/18 (20/40/40/20 µgr of HPV L1 VLP), 3 doses (mo 0-2-6)		
Place	USA	Brazil/Europe/ USA		
Primary endpoint	Virological	Histological		
Participants	2.391 (2392?)	551 (Extension post 3 yrs: 241)	5.442	12.157
	Note: data differ slightly according to source			
Inclusion criteria				
Age	16-23 (if virgin: ≥18)			16-26
HPV	Naïve or not (prior or ongoing HPV infection of any type included)			
Pap smear	No prior abnormal			
Sexual partners	≤4, virgins were enrolled only if seeking contraception.			
Exclusion criteria				
	Pregnancy, no history of genital warts			
Follow-up post first dose	48 months	5 years	3 years	3 years
Procedures				
Pap smear	Every 6 months			Every 12 mo
Referral	ASC-US	ASC-US and/or HPV +		
Statistical analysis				
Per Protocol (PP)	HPV-specific naïve at baseline and up to mo 7. Completed vaccine schedule / no protocol violation. Cases counted from Mo 7.			
(Modified) Intention To Treat (MITT) 1	HPV-specific naïve at baseline and up to mo 7. Completed vaccine schedule. Cases counted from Mo 7			
MITT 2	HPV-specific naïve at baseline. Received at least one dose. Cases counted from Mo 1			
Restricted MITT (RMITT 2)	HPV- specific naïve at baseline, PAP normal at day 1, cases counted from mo 1.			
MITT 3	At least one vaccine dose, cases counted from mo 1.			
Comments	Total enrolled: 20.583; 27% had evidence of exposure to at least one of the 4 vaccine type. (PCR+ and/or seropositive to vaccine HPV type). Participants were **not** tested for other HPV types at enrollment. Sometimes other combinations are used, for example PP + PAP normal at day 1.			

Source: FDA technical documents,[9, 59] and Joura.[58]
Protocol 005: Mao,[62] Koutsky.[61],
Protocol 007: Villa.[65, 66, 37]
Protocol 013: Garland,[63] Joura.[58]
Protocol 015: Future II study group,[39] Joura.[58]

3.5.2 Bivalent vaccine – Cervarix (HPV 16/18)

The bivalent (HPV 16/18) vaccine efficacy has been assessed in one multicentric phase 2 RCT which is still ongoing. Characteristics and results are shown in table 8. Results at 42 months (36 months post dose 3) have been published.[67] An earlier report of this trial did not provide data on CIN 2+ endpoints.[68] The primary endpoint for this study was HPV infection. Although data are given on CIN 2+ endpoints (HPV-specific, and all CIN 2+ regardless of HPV status), the author acknowledges that this study was not powered to show efficacy for histological endpoints. A description is provided in table 8.

Table 8: Phase II RCT of Cervarix vaccine efficacy

Intervention	Bivalent 16/18 (20µg /20µg VLP) , 3 doses 0-1-6 mo
Place	Canada/USA/Brazil; 32 sites
Participants	1113 for initial phase (18 mo then up to 27 mo); 776 for extension to 44-53 months
Primary endpoint	HPV-specific incident infection.
Inclusion criteria for first phase	
Age	15-25
HPV	Cytologically negative and seronegative HPV 16-18 PCR-DNA negative for 14 high-risk HPV types no more than 90 days before study entry
Pap smear	No prior abnormal
Sexual partners	≤6. Virgins only if seeking contraception
Other	No ongoing treatment for external condylomas.
Exclusion criteria	Pregnancy
Inclusion criteria for FU (➔27 mo) (extension)	
	Received all 3 doses of vaccine. Completed initial phase, treatment allocation still blinded, no ablative or excisional therapy of the cervix or hysterectomy after enrollment
FU (mo)	18 mo ➔ extension to 27 mo ➔ extension to 44-53 mo
Statistical analysis	Woman censored from assessment in the extended FU if a defined endpoint associated with HPV 16/18 occurred in the initial efficacy study. Women censored from type-specific assessment if an incident infection associated with any other high-risk HPV type had been detected in the initial efficacy study.
Per Protocol (PP)	HPV-negative for high-risk types at baseline HPV 16-18 negative up to mo 7. Completed vaccine schedule / no protocol violation. Cases counted from Mo 7.
ITT	Received at least one dose + any data available for outcome measurement
Comments	Availability of analyses of women included in extended FU phase vs combined initial and FU phases. Study not powered to estimate efficacy for histo-pathologically confirmed cervical lesions.

Source: Harper.[68, 67]

Interim results from the so-called PATRICIA study - a larger, international phase III RCT have recently been published.[24] A description is provided in table 9.

Table 9: Phase III RCT of Cervarix vaccine efficacy

Intervention	Bivalent 16/18 (20µg /20µg VLP) , 3 doses 0-1-6 mo (assessed against hepatitis A vaccine)
Place	14 countries in Europe, South and North America, Asia.
Primary endpoint	CIN 2+ related to HPV 16 or 18
Inclusion criteria	
Age	15-25
Sexual partners	≤6.
PAP	Normal or low grade cytology (ASCUS or LSIL)
Exclusion criteria	History of colposcopy Pregnant or breast-feeding Chronic or auto-immune disease, or immunodeficiency
Participants	9258 vaccinated / 9267 control (total cohort for efficacy)
FU (mo)	Mean length of follow-up at interim analysis: 14.8 months (pre-specified , event defined, interim analysis)
Statistical analysis	In participants who received at least one vaccine dose (intention to treat) (a) Primary analysis of efficacy against HPV 16/18 CIN 2+ in a subset of total cohort (women uninfected with specific HPV types) 7788 vaccinated / 7838 control (modified intention to treat) (b) Analysis in total vaccinated cohort for efficacy
Comments	Participants seropositive and/or DNA positive at entry: 19 % for HPV 16, 13% for HPV 18. 14/23 cases of CIN 2+ with HPV 16/18 had at least another oncogenic type in the lesion. Attribution of causality in case of multiple oncogenic HPV-types in the lesion: - If presence of an oncogenic HPV infection preceding the development of CIN, the lesion was attributed to this type - in cases of several HPV types in the lesion, and no detection of HPV 16/18 in previous samples, attribution to HPV 16/18 if specific E4 gene expression

Source: Paavonen.[24]

3.5.3 Conclusion

Efficacy of HPV vaccines can be calculated in different trial sub-populations, with very different results. In clinical trials of Gardasil in particular, up to 5 or 6 different populations are defined. Per-protocol (PP), several versions of modified intention to treat (MITT 1, 2, 3), restricted modified intention to treat (RMITT 1, 2), etc,[9] using varying combinations based on:

- HPV status at baseline (HPV naïve or not: naïve at day one or naïve at day one and up to month 7)
- Cytology test result at baseline (normal or not)
- completion of vaccine schedule (at least one dose, or 3 doses)
- time for counting cases (from month one after first dose, vs. from month 7, corresponding to a completed vaccine schedule)

For the sake of clarity, and because of its clinical relevance, we choose to present results based on a distinction between participants HPV-naïve at baseline, or not. Indeed, efficacy in HPV-naïve participants is supposed to approximate more closely the efficacy that could be expected when vaccinating sexually-naïve girls, the primary target

for the current vaccines. Understanding the different definitions of 'HPV-naïve at baseline' is of primary importance to correctly interpret the data.

In Gardasil trials (see table 7) subjects were initially tested only for vaccine-type HPV and they were considered as 'HPV-naïve at baseline' if in addition to being seronegative, and PCR negative for the four vaccine types they also had a normal cytology. These participants are not necessarily 'truly' HPV-naïve as they might still have been infected by other HPV types. HPV-tested subjects were randomized regardless of their HPV status at baseline. Overall, this population included 27% of participants who were positive to at least one vaccine type at baseline. Efficacy in the total randomized population more closely approximates the efficacy that could be expected in real life when vaccinating women similar to trial participants: similar age range and with similar characteristics, in particular regarding previous and current exposure to HPV. Typing of cervico-vaginal specimens for 14 high-risk HPV types has been done *'a posteriori'* but genotyping results have not been published yet. However, the results have been used to define a HPV-naïve population and results were presented at an ACIP meeting in February 2007.[69]

In Cervarix phase III trials participants were tested at baseline for 14 high-risk HPV types but the primary analysis was done in a population naïve for HPV-specific (16/18) types, regardless of status for other HPV types.[24] In the phase II trials, however, only participants naïve to 14 high-risk types were included in the first place.[67]

3.6 EFFICACY ON CIN 2+ ENDPOINTS (CIN 2/3 OR AIS)

3.6.1 Efficacy among subjects HPV-specific naïve at baseline

This population is used in trials to approximate the expected efficacy in sexually-naïve girls, who are the primary target group for HPV vaccines.

3.6.1.1 Gardasil

Combined efficacy data are presented in table 10.

There are no published data on the efficacy of the vaccine against all CIN 2+, regardless of the HPV type involved, in a population HPV naïve at baseline. However, some data are available from the FDA technical document (at 2 years follow-up post dose 1).[9] In the table we also show updated 3-year follow-up data provided by the manufacturer at the February 2007 ACIP meeting, available as a slide show on the CDC website, but not independently reviewed.[69]

Table 10: Combined analysis of Gardasil efficacy on CIN 2+ in subjects HPV-specific naïve at baseline (from different sources)

Gardasil		Placebo		
n/N	**Incidence rate / 100 PY at risk**	**n/N**	**Incidence rate / 100 PY at risk**	**Efficacy (95% CI)**
HPV 16/18 related.[64]				
PP population. HPV-specific naïve up to Mo 7, no protocol violation, cases counted from mo 7.				
1/8579	<0.1	85/8550	0.4	99% (93 to 100)
Any HPV type.				
RMITT2 population naïve to four HPV vaccine types, PAP negative at baseline, at least one vaccine dose, cases counted from mo 1, table 13.[9]				
59/5638	0.5	96/5701	0.8	37.9% (13.2 to 55.9)
PP population. HPV-specific naïve up to Mo 7, no protocol violation, cases counted from mo 7. Table 26.[9]				
54/5051	0.7	66/4887	0.9	20.5% (<0 to 45.5)
RMITT2 population (new definition following a-posteriori retesting of samples): naïve to 14 HPV types, PAP negative at baseline, at least one vaccine dose, cases counted from mo 1[69].				
52/NA	NA	96/NA	NA	46% (24 to 62)

PP: per protocol. (R)MITT: (restricted) modified intention to treat.
Follow-up: 3 years post dose 1.

Table 11 shows the vaccine efficacy specifically for non-HPV 6/11/16/18 related CIN lesions. The reader should be aware that these data are also partially included in the data in table 10 on any HPV type, but different population definitions hamper comparisons. A negative number for VE indicates that more lesions appear in the vaccine group. This could in theory indicate potential genotype replacement, but confidence intervals are extremely wide.

Table 11: Combined analysis of Gardasil efficacy on CIN 2 and CIN 3 not related to HPV 6/11/16/18 in subjects HPV-specific naïve at baseline

Gardasil		Placebo		
n/N	**Incidence rate / 100 PY at risk**	**n/N**	**Incidence rate / 100 PY at risk**	**Efficacy (95% CI)**
*MITT-1 population: HPV-specific naïve up to mo 7, 3 vaccine doses, cases counted from mo 7, includes protocol violators**				
CIN 2: 59/5993	0.7	49/5766	0.6	-16.1% (-73.2% to 21.8%)
CIN 3 36/5993	0.4	27/5766	0.3	-28.5% (<0.0 to 24.1)

For protocols 005, 007, 013, 015.
*Source: FDA slide show, slide 42.[59]
PP: per protocol. (R)MITT: (restricted) modified intention to treat.
Follow-up: 3 years post dose 1.

3.6.1.2 Cervarix

Efficacy data in participants HPV naïve at baseline are available from a phase II trial (up to 4.5 years from Harper[67], results at 5.5 years for the same cohort have been presented as a poster at a conference[70]), and from the interim analysis of a phase III trial.[24] Note that this last publication does not report on overall CIN 2+ incidence regardless of HPV DNA status (see table 12).

Table 12: Cervarix efficacy on CIN 2+ in participants HPV naïve at baseline

	Cervarix		Placebo		
	n/N	**Incidence rate /100 py**	**n/N**	**Incidence Rate / 100 py**	**Efficacy (95% CI)**
Phase II trial (M)ITT population: naïve for 14 high-risk HPV at baseline, at least one dose of vaccine, cases counted from month 1					
Results up to 4.5 year-follow up, Harper et al.[67]					
HPV 16/18 related CIN 2+	0/481	NA	5/470	NA	100% (-7.7 to100.0)
All CIN 2+ (regardless of HPV DNA status)	3/505	NA	11/497	NA	73.3% (-1.0 to 95.2)
Same cohort, 5.5 year follow-up, Gall et al poster presentation.[70]					
HPV 16/18 related CIN 2+	0/NA	NA	7/NA	NA	100% (33 to100)
All CIN 2+ (regardless of HPV DNA status)	5/NA	NA	15/NA	NA	68.0% (7 to 91)
Phase III trial (Paavonen).[24] Population HPV 16/18 negative at baseline. Mean FU 14.8 mo					
HPV 16/18 related CIN 2+	2/7788	0.02	21/7838	0.22	90.4% (53.4 to 99.3)
All CIN 2+ (regardless of HPV DNA status)	NA				

3.6.2 Efficacy among subjects regardless of HPV status at baseline

3.6.2.1 Gardasil

Of all subjects enrolled in the Gardasil RCTs, 27% were positive for at least one of the 4 HPV vaccine types at baseline, and 21% for either HPV 16 and/or HPV 18.

Vaccine efficacy in this population is expected to reflect the proportion of all precancerous lesions, regardless of HPV type, that could be prevented by the vaccine in a population similar to trial participants: sexually active females in a similar age range and with similar characteristics as in the trial. Results are shown in table 13.

Table 13: Combined analysis of Gardasil efficacy on CIN 2+ in subjects regardless of HPV status at baseline.[64]

Gardasil		Placebo		
n/N	**Incidence rate / 100 PY at risk**	**n/N**	**Incidence rate / 100 PY at risk**	**Efficacy (95% CI)**
HPV 16/18 related				
142/10291	0.5	255/10292	0.9	44% (31 to 55)
Any HPV type				
394/10291	1.3	483/10292	1.6	18% (7 to 29)

Protocols 005,007,013,015.
ITT population: regardless of HPV status at baseline, at least one vaccine dose, cases counted from month 1.
Mean follow-up: 3 years post dose 1.

3.6.2.2 Cervarix

No data available.

3.6.3 Efficacy among subjects HPV-specific positive at baseline

3.6.3.1 Gardasil

Some data are available from the FDA technical document. They are presented in table 14. The negative VE indicates that more lesions occurred in the vaccine group.

Table 14: Combined analysis of Gardasil efficacy on CIN 2+ among subjects HPV-specific positive at baseline

Gardasil			Placebo			
N	**n cases /PY at risk**	**IR /100 PY at risk**	**N**	**n cases /PY at risk**	**IR / 100 PY at risk**	**Efficacy (95% CI)**
HPV 6/11/16/18 related						
568	75 /1016.2	7.4	580	69/1044	6.6	-11.7% (<0.0 to 20.6)
any HPV type						
NA						

Protocols 007, 013 and 015.
HPV-positive: PCR positive and seropositive for the relevant HPV type.
Source: FDA technical document, p15. 2 year follow-up.[9]

3.6.3.2 Cervarix

No data available.

3.6.4 Efficacy of Gardasil on CIN 2+ endpoints: discussion and conclusion

Combined data of large trials up to 3 years follow-up have now been published in the scientific literature. We discuss here the external validity of these results and the possible population impact of the vaccine.

3.6.4.1 *Efficacy and population impact in sexually-naïve females*

The vaccine clearly shows a very high vaccine efficacy in preventing precancerous lesions *related to vaccine type HPV strains* (HPV 16/18) in HPV-specific naïve subjects enrolled in the trials. But, it is still unclear what proportion of *all* (pre)cancerous lesions can be prevented by the vaccine in a truly HPV-naïve population such as the primary target group for vaccination, i.e. 12 year old girls.

Table 11 shows that there were more CIN 3 lesions not related to the vaccine type in the vaccine group than in the placebo group. In fact the incidence of disease due to non-vaccine type was 5.5% higher overall in the vaccine group compared to placebo (EMEA scientific report,[8] discussion section, page 29). The manufacturer gave the following explanation orally, during a meeting with the FDA.[71] Quote: *'Published data refer to subjects HPV-specific naïve at baseline but these are not a perfect proxy for sexually-naïve subjects, they might still have been infected by other HPV types and therefore at higher risk for CIN 2+ than a truly naïve subject. The rate of CIN 2+ due to non-vaccine HPV types in this 'not truly naïve' population, will be higher in the first months and thus contribute a disproportionate share of all CIN 2+ during the first months. Also participants identified with HPV-specific infection during the trial were censored. This created a selective bias particularly during the first months because the vaccine provided some degree of protection in the vaccine group even during these 7 months before completing the 3 doses and as a consequence more subjects were excluded from the vaccine group than from the placebo group. As subjects infected with HPV 16/18 are likely to be at higher risk for sexually transmitted diseases in general, and other HPV infections in particular, this created a selective exclusion of high-risk participants from the placebo group, leading to a lower incidence of CIN 2/3 during follow-up in the placebo group.'* (end of quote)

The explanation of a potential selection bias between vaccine and placebo groups seems plausible, but no data are available to evaluate to what extend this explains these data. Another plausible explanation, less favorable for overall 'population' vaccine efficacy, is that genotype replacement occurs in the vaccine group.

The *'a posteriori'* re-testing of all enrolled subjects for 14 high-risk HPV types will allow for a better approximation of the population impact in a more *'truly'* naïve population at baseline. These data have not been published yet but were presented at the February 2007, ACIP meeting. Although not peer-reviewed, we showed them in table 10, as they seem to provide the best currently available estimate of the population impact of Gardasil in a truly susceptible population, corresponding to 12 year old girls,[69] and assuming protection persists until this population becomes sexually active. Under these assumptions, Gardasil could be expected to prevent 46% of all CIN 2+ (95% CI: 24 - 62) during a 3 year follow-up.

3.6.4.2 *Efficacy and population impact in sexually-active females*

Table 14 shows clearly that the vaccine has no efficacy against vaccine-specific histological endpoints, if subjects were already infected with vaccine-specific strains, and it has no efficacy either on infection-related endpoints.[72] Indeed, as stressed repeatedly by the manufacturer, Gardasil was designed to be a preventive vaccine, not a therapeutic vaccine. In trial subjects 16-26 year old sexually active females who had had no more than 4 sexual partners, 27% had been exposed to at least one of 4 HPV types included in the vaccine, and Gardasil prevented no more than 18% (95% CI 7 to 29) of all CIN 2 in this population (see table 13). At population level, the impact of any 'catch-up' immunization strategy of sexually active women will clearly depend on the sexual behavior of this population and their previous and current exposure to HPV. At an individual level, the efficacy of the vaccine is likely to depend on the individual risk of having been exposed. Testing the subject for HPV-specific strains might potentially orient clinical decision making, but solid evidence for this strategy is lacking and this is clearly not the preferred strategy for the companies involved.

3.6.5 Efficacy of Cervarix on CIN 2+ endpoints. Discussion and conclusion

Results for Cervarix seem to confirm the high efficacy of the bivalent vaccine against cervical dysplasia associated with HPV vaccine strains. Cervarix studies have also confirmed the high prevalence of multiple infections with oncogenic HPV types in cervical dysplasia. For instance 21 CIN 2+ with HPV 16 or 18 DNA in the lesion were found in the control group, 12/21 included also other oncogenic HPV types. This underlines again the importance of measuring vaccine efficacy on *all lesions* (regardless of HPV type involved) because the possibility of strain replacement is obviously there. Unfortunately, data on overall vaccine efficacy available for Cervarix are only available from phase II trials, which were not designed, and therefore lack power, for evaluating such endpoints.

3.7 EFFICACY ON EXTERNAL GENITAL LESIONS (GARDASIL ONLY)

The term External Genital Lesions (EGL) comprises endpoints such as condylomas and vulval or vaginal pre-cancerous lesions. For these endpoints only data for Gardasil can be presented.

Phase III trial data on Gardasil efficacy in preventing vulval and vaginal endpoints as well as condylomas have been published for protocol 13.[63] A combined analysis of protocols 007, 013 and 015 focusing on vulval and vaginal endpoints is also available.[58] Data from a combined analysis of the efficacy of Gardasil on condylomas are also available from the FDA technical report.[9]

Given the very different clinical implications of these endpoints, we present data separately for condylomas, and data on VaIN 2+ and VIN2+.

3.7.1 Efficacy among subjects HPV-specific naïve at baseline

Table 15 Gardasil efficacy on condylomas in subjects HPV-specific naïve at baseline. Per protocol population.

	Gardasil			Placebo			
Source	**N**	**n cases**	**IR /100 PY at risk**	**N**	**n cases**	**IR / 100 PY at risk**	**Efficacy (95% CI)**
HPV 6/11/16/18 related							
Protocol 013 3 year FU*	2261	0	0.0	2279	48	0.9	100% (92-100)
Combined 007, 013, 015 2 year FU**	7897	1	0.0	7899	91	0.8	99% (94-100)
Any HPV type							
NA							

Sources: * Garland,[63] ** adapted from EMEA technical document, page 26.[8]
PP population: HPV-specific naïve at baseline and up to mo 7, cases counted from month 7, no protocol violation.

Table 16: Combined Gardasil efficacy on vulval (VIN 2+) and vaginal (VaIN 2+) endpoints in subjects HPV-specific naïve at baseline

Gardasil			Placebo			
N	**n cases**	**IR /100 PY at risk**	**N**	**n cases**	**IR / 100 PY at risk**	**Efficacy (95% CI)**
HPV 16/18 related*						
PP population (naïve to vaccine-type HPV at baseline and up to mo 7, 3 vaccine doses, did not deviate from protocol, cases counted from month 7) 3 years FU						
7811	0	0.0	7785	15	0.01	100% (72-100)
Any HPV**						
RMITT 2 population (naïve to vaccine type at baseline, at least one vaccine dose, Pap test normal at day 1, cases counted from mo 1), 2 years FU						
5734	5	0.04	5769	27	0.2	81.3% (50.8 - 94.4)

Protocols 007, 013, 015.
Sources: *Joura,[58] ** FDA slide show , slide 51.[59]

3.7.2 Efficacy among subjects regardless of HPV status at baseline

Table 17: Combined Gardasil efficacy on condylomas in subjects regardless of their HPV status at baseline

Gardasil			Placebo			
N	**n cases**	**IR /100 PY at risk**	**N**	**n cases**	**IR / 100 PY at risk**	**Efficacy (95% CI)**
HPV 6/11/16/18 related						
MITT 3 population: regardless of HPV status at baseline at least one vaccine dose, cases counted from mo 1						
8954	88	0.3	8962	184	1.0	68.5% (57.5 - 77.0)
Any HPV						
NA						

Protocols 007, 013, 015. MITT 3 population.
Source: FDA slide show slide 49.[59]

Table 18: Combined Gardasil efficacy on vulval (VIN 2+) and vaginal (VaIN 2+) endpoints in subjects regardless of their HPV status at baseline

Gardasil			Placebo			
N	**N cases**	**IR /100 PY at risk**	**N**	**n cases**	**IR / 100 PY at risk**	**Efficacy (95% CI)**
HPV 16/18 related						
9087	9	0.03	9087	31	0.12	71% (37-88)
Any HPV						
9087	27	0.10	9087	53	0.2	49% (18-69)

Subjects with at least one vaccine dose, cases counted from month 1 (ITT population), protocols 007, 013, 015. Mean FU: 3 years
Source: Joura.[58]
ITT population: all randomized.

Five cases of VIN 2/3+ or VaIN2/3, all in the placebo group, were found to be associated to HPV 6; none was associated to HPV 11.

Out of 53 cases observed in the placebo group, 33 were VIN 2/3 and 21 VaIN 2/3. Out of 33 VIN 2/3, 21 (64%) were HPV 16 related.

3.7.3 Efficacy among subjects HPV-specific positive at baseline

No information available.

3.8 EFFICACY OF HPV VACCINE IN MALES AND IN PRE-ADOLESCENT GIRLS AND BOYS

Females who are naïve for the vaccine HPV types are expected to benefit most from the vaccine, but efficacy studies cannot be conducted in pre-adolescent girls for reasons outlined previously. Under the assumption that similar humoral immunogenicity would imply similar efficacy, studies comparing immunogenicity between adolescent girls and adult women allow 'bridging' efficacy from adult women to adolescent girls.

The rationale for immunizing males (boys) is twofold: the prevention of HPV-related morbidity (such as condylomas, penile or anal cancers) in the subjects themselves but also depleting the virus reservoir by interrupting the transmission of vaccine HPV strains (herd immunity).

3.8.1 Gardasil

We found no data on the efficacy of HPV vaccines in adult males, neither clinical efficacy, nor prevention or infection, nor immunogenicity but trials of Gardasil in males are underway. However, we found 2 published studies reporting on Gardasil induced humoral immunity in pre-adolescent girls and boys, so called 'bridging studies', described in table 19.

Table 19: Studies reporting on Gardasil-induced immunity in pre-adolescent girls and boys

Source	Data on girls	Data on boys	Follow-up post dose 1
Block et al.[73] Protocol 016	Comparing immunogenicity between girls and young adult women ('bridging' study)	Comparing immunogenicity between boys and young women	7 mo
Reisinger et al.[74] Protocol 018.	Comparing immunogenicity between boys and girls		18 mo

The FDA website did not provide additional data but confirmed this information. A description of the bridging study by Block et al. is presented in table 20.

Safety data are addressed later in this chapter.

Table 20: Gardasil, description of bridging study

Design	Prospective cohort study. Age and gender stratified, non inferiority study comparing immunogenicity one month after completing 3 doses of HPV 6/11/16/18 vaccine (given at month 0-2-6). Recruitment at 61 clinical centers in Asia, Australia, Europe, Latin-America, and North America.
Groups compared	Adolescents 10-15 years old, sexually naïve, generally healthy. 482/506 girls and 483/510 boys enrolled completed vaccination and completed study. Women 16-23 years old. Sub-study within protoc 007 (see inclusion criteria above). 465/513 enrolled completed vaccination and completed study.
Measure of immunogenicity	Neutralizing anti-HPV antibodies. HPV type-specific competitive immuno-assay (cLIA). Scales specific to type (cross-away comparisons not valid). Outcomes: Ratio of GMT, and % seroconversion at month 7 (4 weeks after third dose), per HPV type. Girls vs. women; boys vs. women
Analysis	Per protocol population: received 3 doses within pre-specified visit intervals, no protocol violation, seronegative for specified type at day 1 (➔ numbers in PP population are type-specific.). For adult women: PCR-negative up to month 7 for specific HPV type. Analysis adjusted for region.
Note:	Biological samples coded to maintain analyst blinding.

Source: Block et al.[73]

In the study of Block et al., the GMT of neutralizing antibodies was certainly not inferior, and even higher in adolescent girls and boys, as compared to adult women (table 21). This higher immunoreactivity in younger ages was anticipated and has been documented previously for viral hepatitis vaccines.[75]

Table 21: Gardasil, Ratios of GMTs in fully vaccinated girls and boys vs. women at month 7 after first dose

Assay (cLIA)	N Evaluated			GMT Ratio (95% CI)	
	Girls	Boys	Women	Girls/women	Boys/women
Anti-HPV 6	423	428	320	1.67 (1.46-1.91)	1.81 (1.58-2.08)
Anti-HPV 11	423	428	320	1.73 (1.50-2.00)	1.87 (1.60-2.17)
Anti-HPV 16	424	427	306	1.84 (1.54-2.20)	2.21 (1.84-2.66)
Anti HPV 18	426	429	340	2.02 (1.71-2.39)	2.68 (2.24-3.19)

Source: Block et al.[73]

At 18 months, specific neutralizing antibodies were 4 to 6 times less than the peak response at 7 months (table 22).

Table 22: Gardasil, GMTs in fully vaccinated girls and boys: at month 7 vs 18 after first dose

Assay (cLIA)	7 months				18 months				GMT ratio 7mo/18 mo	
	Boys		Girls		Boys		Girls		Boys	Girls
	N	GMT	N	GMT	N	GMT	N	GMT		
Anti-HPV 6	456	1007	492	808	449	227	481	213	4.4	3.8
Anti-HPV 11	457	1334	492	1187	540	292	481	300	4.6	4.0
Anti-HPV 16	455	6316	489	4490	448	1402	478	1250	4.5	3.6
Anti HPV 18	458	1581	494	1071	451	233	483	181	6.8	5.9

Source: computed from data reported in Reisinger et al.[74]

The general conclusion is that there are enough data to support non-inferiority of vaccine-induced humoral immunity in girls, and boys, as compared to young women such as those included in clinical trials of Gardasil efficacy. In both boys and girls, GMTs at month 18 were approximately 4 to 7 fold lower than the GMTs observed at month 7.

3.8.2 Cervarix

We found no data on males.

One study has been published that compared immunogenicity of Cervarix in a group of females 10-14 years old (N=158) with immunogenicity in females 15-25 years (N=458).[76] GMT ratios are not given, but the study concluded to the non-inferiority of the immunologic response in young girls at 7 months post dose 1.

3.8.3 Discussion / conclusions

It is not known whether raised levels of serum specific neutralizing antibodies are indeed a good correlate of the protection offered by the vaccine. However, given that efficacy studies cannot be conducted in young girls, the information on the possible clinical efficacy of the vaccines in this population seems as good as it can be before the first vaccinated cohorts can be properly evaluated, which will require at least another 10 years.

There are no data on the clinical efficacy of HPV vaccine in males. HPV immunization of young boys is proposed by some not for its putative clinical efficacy but as a way to decrease the transmission of vaccine-strains HPV. This rests on untested assumptions that HPV vaccines could reduce the prevalence and incidence of HPV-specific infection in males as they do in females.

3.9 DURATION OF PROTECTION

If not otherwise stated, months are counted from the first injection, where month zero corresponds to the first dose of vaccine or placebo.

3.9.1 Gardasil

Mean follow-up in the combined analysis of Gardasil efficacy was 3 years. Published data on HPV-specific infections, and immune response, are available for 241 women followed-up for 60 months (54 months after third dose).[37] In the PP population there were 1/104 and 22/120 cases of persistent HPV-specific infection or disease in the vaccine and the placebo group respectively corresponding to a vaccine efficacy for this endpoint of 95.1% (95% CI: 69.4 - 99.9%). The only case in the vaccine group occurred at month 18. At month 24, only 68% remained seropositive for HPV 18 as measured in specific neutralizing antibodies. However, the efficacy for prevention of HPV 18-related high-grade lesions was maintained at 100%.[39] In a modelling study, HPV 16 antibody levels were predicted to remain at levels higher than after natural infection for 12 years in 50% of vaccinees or nearly life-long, depending on the model used.[77] However, further follow-up is needed to clarify the role of antibody levels as a correlate of protection.

3.9.2 Cervarix

Published data are available for 606 women followed-up for 4 years (mean FU time: 47.7 months, SD 3.4, corresponding to 42 months after dose 3). Only HPV-specific endpoints (infection, immunogenicity) are presented for this length of follow-up. No data on histological endpoints are available.[67,a]

In the PP population (completed vaccine schedule, HPV-specific naïve up to mo 7, cases counted from month 7), 0/311 participants in the vaccine group vs. 7/295 participants in the placebo group, experienced at least one persistent HPV 16/18 infection (12-month

[a] As noted before, histological endpoints in Harper's study are available for a population combining participants enrolled in the initial study period and those enrolled in the extended follow-up, but not separately for those enrolled in the extended follow-up period.

definition). Thus vaccine efficacy for this endpoint over 41 months was 100% (95% CI: 33.6 to 100.0).

Results up to 5.5 years for the same cohort have been presented as a poster at a conference.[70]). However these data pool together participants with different length of follow-up (see earlier).

3.10 SAFETY

3.10.1 Gardasil: clinical trial data

Pooled data on adverse events are not presented in the combined analysis of protocols 005, 007, 013, 015 recently published,[64] but are available from the FDA technical documents (with the addition of protocol 018).[9]

We choose to present these rather than data from separate protocols from published studies, since large sample sizes are necessary to achieve sufficient power to study infrequent adverse events.

Separate data for pre-adolescent boys and girls (published) are available from protocol 018,[74] which compared the safety and immunogenicity of Gardasil in boys and girls to a non-aluminum containing placebo.

3.10.1.1 All subjects

SERIOUS ADVERSE EVENTS (SAE)

Table 23: Combined analysis of serious adverse events (SAE) and deaths in Gardasil trials

Subjects with:	Gardasil N=11 778	Placebo N=9 680	Absolute risk difference (95% CI) per 10 000
Serious adverse events over study period	101 (0.9%)	97 (1.0%)	-14 (-40 to 11)
Serious adverse events reported 1-15 days after an injection	53 (0.45%)	42 (0.43%)	2 (-16 to 19)
Deaths	11	7	2 (-6 to 10)

Protocols 007, 013, 015, 016, 018. Source: FDA technical document p21.[9]

A review of serious adverse events (SAE) and deaths that were observed in subjects randomized to Gardasil did not show any safety signal of concern.[9] However, the numbers in those trials are too small for a meaningful comparison of safety aspects.

Moreover, these results are for trial participants only and do not necessarily apply to young girls that are the main target group for this vaccination. More long-term follow-up data on safety are being collected through large post-marketing programs as requested by both the FDA and EMEA.

OTHER ADVERSE EVENTS

Some subjects were requested to keep intense diary cards (detailed safety population). Subjects randomized to Gardasil had a greater incidence of moderate to severe injection site reactions, see table 24. Systemic adverse reactions are shown in table 25.

Table 24: Combined analysis of subjects reporting injection site adverse events experience in Gardasil

Injection site adverse reactions	Gardasil N=6 160	Placebo N=4 064
Subjects with injection site experiences	5 030 (82.9%)	2 927 (73.3%)
Mild	3 162 (52.1%)	2 125 (53.2%)
Moderate	1 586 (26.1%)	724 (18.1%)
Severe	271 (4.5%)	76 (1.9%)

Detailed safety population. Protocols 007, 013, 015, 016, 018. Source: FDA technical document p22.[9]

Table 25: Combined analysis of subjects reporting systemic adverse reactions (frequency ≥ 2%) or greater in Gardasil trials

Systemic adverse reaction	Gardasil N=6 160	Placebo N=4 064
Subjects reporting systemic adverse reaction	3 591 (59.2%)	2 414 (60.4%)
Headache	1 602 (26.4%)	1 101 (27.6%)
Pyrexia	782 (12.9%)	440 (11.0%)
Nausea	370 (6.1%)	251 (6.3%)
Diarrhea	224 (3.7%)	144 (3.6%)
Nasopharyngitis	353 (5.8%)	245 (6.1%)
Pharyngolaryngeal pain	266 (4.4%)	190 (4.8%)
Dizziness	214 (3.5%)	142 (3.6%)
Skin disorder	210 (3.5%)	143 (3.6%)
Abdominal pain upper	193 (3.2%)	136 3.4%)
Influenza	192 (3.2%)	154 (3.9%)
Dysmenorrheal	178 (2.9%)	152 (3.8%)
Abdominal pain	157 (2.6%)	82 (3.2%)
Fatigue	156 (2.6%)	85 (2.1%)
Vomiting	147 (2.4%)	81 (2.0%)
Injury, poisoning, procedural complications	143 (2.4%)	85 (2.1%)
Myalgias	119 (2.0%)	81 (2.0%)

Detailed safety population. Protocols 007, 013, 015, 016, 018. Ref: FDA technical document p22.[9]

3.10.1.2 Adverse events in adolescent boys and girls

No separate data are available from the FDA technical documents (safety data from studies of the vaccine among girls and boys are pooled with data from older participants and presented above).

No formal comparisons between genders were done in the study by Reisinger et al.,[74] see table 26.

Table 26: Gardasil adverse events within 15 days post dose 1, 2 and 3 (cumulative) in pre-adolescent girls and boys

	Gardasil	Non-aluminum containing placebo
Subjects with follow-up	1 165	584
N (%) subjects with		
One or more AE	963 (82.7)	392 (67.1)
Injection site AE	867 (75.3)	292 (50.0)
Systemic AE	541 (46.4)	260 (44.5)
Serious AE	5 (0.4)	0 (0.0)
Serious vaccine-related AE	0 (0.0)	0 (0.0)

Source: Reisinger et al.[74]

EMEA analyses pooled safety data from protocols 016 and 018 separately for boys and we show these results in table 27.

Table 27: Combined analysis of Gardasil adverse events for male subjects 9-15 year old at study enrolment

	Gardasil	Placebo
Subjects with follow-up	1 056	269
Adverse experience:		
Mild	437 (41%)	96 (36%)
Moderate	313 (30%)	60 (22%)
Severe	108 (10%)	15 (6%)
Unknown	12 (1%)	2 (0.7%)

Protocols 016-018. Source: EMEA scientific discussion, p35.[8]

A comparison of adverse events between girls, boys, and women is available from a bridging study,[73] and shown in table 28.

Table 28: Gardasil: clinical adverse events during day 1 to 15 post dose 1, 2 and 3 (cumulative) among girls, boys, and women

	Girls N=501 (100%)	Boys N=500 (100%)	Women N=497 (100%)
Participants with			
Vaccine related injection site adverse event	405 (81%)	370 (74%)	435 (88%)
Vaccine related systemic adverse event	154 (31%)	136 (27%)	160 (32%)
Serious adverse event	1 (0.2%)	1 (0.2%)	0 (0.0%)

Source: Block et al.[73]

3.10.2 Gardasil: post marketing surveillance data

Approximately 5 million doses of the Gardasil had been distributed in the U.S. through March 2007.[60] The US Vaccine Adverse Events Reporting System (VAERS) which compiles reports of adverse events, has computed an overall vaccine adverse events of 33/100 000 doses, and of serious adverse events (SAE) of 1.8/100 000 doses; 13 cases of Guillain-Barre have been reported.[78] These cases are being investigated,[79] and continued monitoring is ongoing.

Well-known limitations of passive surveillance include underreporting, stimulated reporting due to media attention and other factors, and lack of availability of denominator data.

3.10.3 Cervarix

In the PATRICIA trial a safety subset of more than 3 000 women has completed and returned safety diary cards documenting symptoms experienced during the 7 days after vaccination, and within the first 30 days after vaccination.[24]

The overall rate of severe adverse events was 3.5%, similar in the HPV vaccine and in the control group (hepatitis A vaccine).[24] Pain was the most common adverse event (90.5% in the HPV vaccine group vs. 78.0% in the control group). Grade 3 pain (preventing normal, everyday activities) occurred in 16.3% of participants randomized to the HPV vaccine, and in 4.4% of participants randomized to the hepatitis A vaccine.

No safety data were found on FDA or EMEA websites since the product is not approved by the FDA yet, and because, even while it received a positive opinion from EMEA in July 2007, the EPAR was not publicly available until October 2007.[15]

3.11 GENERAL CONCLUSIONS ON EFFICACY AND SAFETY OF HPV VACCINES FOR GARDASIL

3.11.1 Summary of current evidence

Large trials with around 20 000 sexually active females provide combined data available up to 3 years FU.

Since overall efficacy, regardless of HPV type, is the most relevant measure of efficacy for public health, we summarize the information available in that respect in table 29. A comparison of Gardasil efficacy on HPV-specific cervical endpoints, and on endpoints regardless of the HPV type, is presented in table 30 (summary of the evidence presented in this chapter).

Table 29: Baseline risks and best estimates of Gardasil efficacy on various clinical endpoints, regardless of the HPV type involved

	Sexually-naïve subjects*		Sexually active subjects 16-26 year**	
Outcome	**Baseline risk (when becoming sexually active)**	**Vaccine efficacy**	**Baseline risk**	**Vaccine efficacy**
CIN 2+	0.8 / 100 py	46% * (24-62)	0.9/100 py	18% (7-29)
VIN2+/VaIN2+	0.2 / 100 py	81% (51-94)	0.2/100 py	49% (18-69)
Condylomas	At least 0.8/100 py	NA	At least 1.0/100 py	NA

*Approximated by results observed in unexposed trial participants. **Approximated by results observed in all trial participants. Pooled trial data, intention to treat analysis.
Sources: Ault,[64] and Manufacturer data.[69]

Table 30: Best estimates of Gardasil efficacy: HPV specific vs. any cervical endpoint

Target group Outcome	Sexually-naïve subjects*	Untested sexually active subjects 16-26 year**
CIN 2+ - HPV- specific	99% (93-100)	44% (31-55)
CIN 2+ - all (population impact)	46% *** (24-62)	18% (7-29)

*Approximated by results observed in unexposed trial participants. **Approximated by results observed in all trial participants. Note that females who had had more than 4 sexual partners were excluded from these trials. *** Data from manufacturer.[69]

The risk of developing high grade cervical dysplasia (CIN 2+) for girls such as those targeted for vaccination (once they become sexually active) is 8-9 per 1 000, and per year. In the best case scenario, HPV vaccination could lower this risk to around 4 per 1 000 and per year.

Similarly the individual risk of high grade vulvar or vaginal dysplasia (VIN2+ or VaIN2+) is 2 per 1 000, and per year. In the best case scenario, HPV vaccination of unexposed females could lower this risk to around 4 per 10 000 and per year.

There are no data on the overall efficacy of Gardasil in preventing condylomas, but the vaccine had 100% efficacy on HPV-specific condylomas.

In females previously exposed to HPV vaccine strains (as demonstrated by HPV testing) there is no evidence of efficacy of the vaccine, and this is the main reason why overall efficacy on dysplasia (CIN 2+) in an untested, sexually active population (combining exposed and unexposed females) is low (18% in clinical trials). This figure is relevant when assessing the possible impact of a population-based catch-up vaccine strategy (with population-based risk assessment, rather than individual-based risk assessment).

The humoral immune response in girls and boys does not appear to be inferior to the immune response in young women. With the currently available data there are no major safety concerns.

3.11.2 Major uncertainties

Major uncertainties for the assessment of vaccination strategies remain. Length of follow-up is limited, and efficacy data relate to precancerous lesions, not to the various types of cancer that the vaccine intends to prevent. The duration of protection after 5 years is unknown, and therefore the need and efficacy of a booster vaccination cannot be properly assessed. The long-term impact of the vaccine on the epidemiology of HPV infections remains uncertain: the possibility of strain interaction, strain replacement that might significantly decrease the benefit of the vaccine, or at the contrary cross-protection that might positively influence VE. The large confidence intervals around efficacy results can accommodate all these possibilities. Finally, the efficacy in males and in particular the efficacy in preventing infection has not been documented. As for any new product, long-term safety is also unknown, but no serious safety concern exist at this stage

3.11.3 Discussion

3.11.3.1 Short term versus long term benefits of the vaccine

The benefits to be expected from HPV vaccines can be divided into short-term and long-term outcomes. For obvious methodological reasons efficacy data are limited to short-term outcomes (prevention of high grade dysplasias, condylomas for Gardasil), for which there is sufficient evidence of efficacy. Major uncertainties relate to benefits expected only in a distant future (prevention of cervical, vulvar, vaginal cancer etc).

In countries where screening activities are performed, short-term outcomes (reduction in CIN 2+) matter a great deal because cervical dysplasias are identified and treated, and treatment is invasive and involves some serious risks, such as premature delivery at subsequent pregnancies.[48] In fact the better the coverage of the screening programme, the more important will be the short-term benefits of the vaccine. When a higher proportion of CIN 2+ are found through screening, more local cervical therapies can be avoided by the vaccine, but less cancers will occur (due to screening) and therefore the absolute number of cancers avoided by the vaccine will decrease in the long-term. As for condylomas (Gardasil only), these are not a life-threatening condition but they are difficult to treat and still involve serious morbidity.

In countries were screening activities are not performed (and therefore where dysplasias are not identified and treated, and where therefore cervical cancer incidence is higher), the long-term benefits matter much more, and the uncertainties concerning long-term benefits of the vaccine are even more important.

3.11.3.2 Identifying those more likely to benefit from the vaccine

The vaccine only benefits those who have not yet been infected with the HPV-specific vaccine strains. It is relatively easy to identify unexposed *populations* who could benefit from the vaccine (population of young girls at an age where the vast majority has not yet become sexually active, for instance 12 year). In older persons (in the age group 16-26 for instance, such as those included in vaccine trials), identifying those most likely to benefit from the vaccine should ideally be identified through an individual assessment of the risk of previous exposure to HPV-specific vaccine strains. Without HPV testing, this involves a subjective and imperfect assessment based on the number of previous sexual partners, taking into account that the probably of exposure is high, even with the first sexual partner.

The strategy to define type 16/18 HPV-naïve subjects as done in clinical trials could theoretically also be applied in routine practice. It remains unclear which of the currently marketed tests would be more appropriate and what the acceptability of such a strategy would be.

3.11.4 Conclusions

There are enough data to conclude that Gardasil can reduce the rate of high-grade cervical dysplasia, in females not previously exposed to HPV-specific vaccine strains, by 46% (95% CI 24 - 62), which could result in a corresponding decrease in excisional or ablative procedures. Testing sexually active females for previous exposure to HPV vaccine strains is not routine practice.

There is currently no safety signal associated with Gardasil vaccination but current large post-marketing surveillance programmes need to provide additional information on potential safety issues.

It is not yet known if protection extends longer than 5 years, and a booster might be needed at some point in the future. Major uncertainties relate to the long term impact of the vaccine on the epidemiology of the virus and on its long term impact on preventing cancer itself.

3.12 CONCLUSIONS ON EFFICACY AND SAFETY FOR CERVARIX

Data on the efficacy and safety of Cervarix are still insufficient to draw definite conclusions, as only interim analyses of a phase III trial are available. Preliminary data show a vaccine efficacy on CIN 2+ related to vaccine strains similar to that of Gardasil , but follow-up is short (14 months) and we could not find any data on vaccine efficacy in reducing overall CIN 2+ regardless of HPV strain involved (except data from a phase II trial). Although we asked the company, we were unsuccessful in retrieving those data directly. Also in the European Public Assessment Report that was made public in October 2007, this information was not available.[15]

Key points

- **Gardasil vaccine targets HPV strains 6/11/16/18. Cervarix vaccine targets HPV strains 16/18.**
- **For Cervarix, only interim analyses of phase III trials have been published (at 13 months). Therefore not enough data are yet publicly available for a proper evaluation (some additional data are expected in the near future through the forthcoming EMEA assessment).**

Gardasil: what we currently know

- **In 16-26 year-old, not HPV infected females (i.e. PCR and / or seronegative for 14 high-risk strains), Gardasil reduces by 46 % (95% CI: 24-62) the rate of high grade cervical dysplasia.**
- **In 16-26 year-old, naïve to HPV vaccine type at baseline, Gardasil reduces by 81% (95% CI: 51-94) the rate of high grade vulval and vaginal dysplasia.**
- **There is no evidence of efficacy in females infected with HPV-specific vaccine strains.**
- **There is no inferiority of the humoral immune response observed in young girls, when compared to young female adults.**
- **There is no important safety issue detected for Gardasil based on the trials.**

Gardasil: what we currently do not know

- **Duration of protection after 5 years and the potential need for a booster vaccination.**
- **Long term impact of the vaccine on the epidemiology of the virus (possibility of strain replacement) which could significantly alter the efficacy of the vaccine on pre-cancerous lesions.**
- **Vaccine efficacy in the long term in reducing cancer itself, as cancer lesions frequently harbour multiple oncogenic HPV strains (including other than vaccine-strain).**
- **Since safety of the vaccine was mainly studied in adult trial populations, the safety in young girls (or boys) is largely unknown, although there is currently no safety issue detected. More long-term data in the target population will be needed to fully evaluate the safety profile of this vaccine for this target population. Those data are currently collected through large-scale post-marketing surveillance.**

4 COST EFFECTIVENESS OF HPV VACCINATION: REVIEW OF THE LITERATURE

4.1 LITERATURE SEARCH

The search for the economic literature around HPV vaccination was performed by identifying, via personal contacts and HTA websites,[80, 81] the most recent HTA reports on HPV vaccination up to May 2007 and by retrieving the relevant citations on health economics and modelling from the reference lists of those reports.[81, 82] Also the reference lists of articles so identified were checked to detect additional relevant citations. The search was closed on May, 1st, 2007.

All articles dealing with the economic aspects of HPV disease or vaccine were collected. Models of HPV infection and disease alone were disregarded. Economic articles were screened based on their abstract and full-text to select only the full economic evaluations of HPV vaccination (i.e. the economic evaluations comparing at least two alternative treatments in terms of both their costs and outcomes, see appendix). Six full economic evaluations of HPV vaccination programmes published before May 2007 have been identified,[83-87, 82] and are summarized in the appendix.

We provide here a critical assessment of the 6 articles published before May 2007, partly based on three recently published reviews of the literature.[88, 89, 52]

Since our most recent literature search, 3 new economic evaluations of HPV vaccination have become available. These articles are not included in the evidence tables of the current review but their results are nevertheless briefly discussed where appropriate.[90-92]

4.2 OVERVIEW OF THE ECONOMIC EVALUATIONS OF HPV VACCINATION

The characteristics of the original 6 economic evaluations of HPV vaccination are summarized in table 31. The assessment of the economic impact of HPV vaccination is a recent topic since all articles are published after the year 2003 when corporate strategies to develop a vaccine became apparent. With the exception of the Norwegian report,[82] all analyses are performed for the USA. The three more recent studies were in Canada,[90] Brazil,[91] and Denmark.[81] As the Brazilian study concerns a setting that is not comparable to the Belgian situation, given the absence of an effective cervical screening programme in Brazil, we excluded this study. Without screening as an effective strategy against cervical cancer, it becomes more likely (but not certain) that vaccination is found to be more cost-effective.

Table 31: General characteristics of the economic evaluations of HPV vaccination

Author	Publication year	Country	Analysis	Timeframe[a]	Discount rate[b]	Perspective	
						Outcome	Cost
Sanders et al.	2003	USA	CUA CEA	Lifetime	3%	QALY LY	Direct medical costs
Kulasingam et al.	2003	USA	CEA	73 yrs	3%	LY	Direct medical costs
Goldie et al.	2004	USA	CUA	Lifetime	3%	QALY	Direct medical costs Time costs
Taira et al.	2004	USA	CUA CEA	38 yrs	3%	QALY LY	Direct medical costs
Elbasha et al.	2007	USA	CUA	Lifetime	3%	QALY	Direct medical costs
Neilson et al.	2007	Norway	CUA CEA	52 yrs	4%	QALY LY	Direct medical costs

a. From 12-years-old; b. Discount rate for both costs and outcomes; CUA: cost-utility analysis; CEA: cost-effectiveness analysis; QALY: quality-adjusted life-years; LY: life-years

4.2.1 Study types and designs

All but one[83] study perform a cost-utility analysis in their base-case, with outcomes expressed as quality-adjusted life-years gained (QALYs).

Three studies use static (cohort) models to simulate the course of HPV infection.[83-85] In those models the force of infection (i.e. the per susceptible rate of infection) remains constant with time so that herd immunity effects are ignored. Two studies use a dynamic model,[87, 82] in which the force of infection varies according to the number of infectious individuals in a population. Herd immunity effects are thus accounted for in those models, i.e. the indirect protection conferred to a population given that susceptible individuals bypass the infectious stage and become immune through vaccination. Taira et al.[86] use a hybrid model, in which the HPV transmission dynamics are simulated (dynamic modelling part) but applied to a single cohort of interest (static modelling part). Compared to dynamic models, static models are likely to underestimate the benefits and the cost-effectiveness (too high ICERs) of HPV vaccination as the contribution of herd immunity is ignored. Static models are further limited by the type of questions they can address. In this context, dynamic models thus appear to be more appropriate since they are able to examine the effects of herd immunity and the possibility for universal (boys and girls) and catch-up vaccination. Such models however are extremely data-demanding and hard to populate realistically.

4.2.2 Population

All studies assume that three doses of the HPV vaccine would be administered to 12-year-old girls. The addition of catch-up strategies or vaccination of boys to the vaccination programmes is investigated in two studies.[86, 87]

4.2.3 Intervention

The vaccine assumptions are shown in table 32. In the two oldest studies,[83, 84] the vaccine is targeted against various HPV types. In the most recent studies, vaccine efficacy is modelled as a reduction in HPV infection (or persistent infection)[85] caused by the HPV 16&18 strains.[85, 86, 90, 81, 87, 82] In Elbasha et al.[87] and the more recent Brisson et al.[90] efficacy against HPV 6&11 infections (the types responsible for genital warts) is also considered in addition to strains 16&18. Note that for the first 4 studies mentioned in the tables, only preliminary data from a phase 1 study,[93] and intermediate results from a phase 2 study,[61] on vaccine efficacy were available at the time of writing.

Table 32: Vaccine assumptions

Author	HPV strains covered	Efficacy[a]	Coverage	Efficacy duration	Booster	Vaccination cost (€ 2006)[b]
Sanders et al.	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	75%	70%	10 yrs	Every 10 yrs	293 €
Kulasingam et al.	70% of high-risk	90%	100%	10 yrs	No	195 €
Goldie et al.	16, 18	90%	100%	Lifelong	No	362 €
Taira et al.	16, 18	90%	70%	10 yrs	Every 10 yrs	293 €
Elbasha et al.	6, 11, 16, 18	90%	70%[c]	Lifelong	No	318 €
Neilson et al.	16, 18	90%	90%	10 yrs	At 22 yrs	[d]373 €

a. Efficacy against the HPV strains covere; b. Cost of 3 doses of the vaccine plus administrations costs; c. Gradual increase of the coverage rate during the fist 5 years of the vaccination programme; d. Administration costs not included; ; yrs: years

4.2.4 Comparator

Screening assumptions are shown in table 33. With the exception of Kulasingam et al.[83], all studies assess the impact of adding HPV vaccination to the current screening practice. Surprisingly, there does not seem to be a consensus between the US studies about current screening programme. In the base-case, Sanders et al.[84] and Taira et al.[86] assume that 71% of young women are screened every 2 years. The assumed screening frequency is higher in Goldie et al.[85] with 71% of women screened every year. In Norway, the current strategy is defined as screening every 3 years women aged 25 to 69 years, with a coverage rate of almost 80%.[82] The adequate modelling of the screening practice is crucial since the cost-effectiveness of a HPV vaccination programme will be highly dependant on the efficiency of the screening programme in place.

In Kulasingam et al.[83] and Goldie et al.[85] the potential for optimising the current screening practice (by varying the screening start age and frequency) is explored and each HPV vaccination plus 'optimal' screening scenario is compared with the next best strategy. It is important to note that the coverage rate of the 'optimal' screening scenarios is always set at 100%.

The test used for routine cytological screening is the conventional Pap smear in most studies. Only two studies report the use of liquid-based tests.[85, 87] The test sensitivity and specificity for detecting squamous intraepithelial lesions vary slightly between the studies: sensitivity from 51% [84, 86] to 66%[85] and specificity from 94%[87] to 97%.[84-86] Kulasingam et al.[83] and Neilson et al.[82] report test characteristics for detecting CIN 2+ (sensitivity 55.6 – 63.0%, specificity 90.0 – 95.7%).

Table 33: Screening assumptions

Author	Current screening practice			Cervical cytological screening		
	Start age	Periodicity	Coverage	Type	Sensitivity	Specificity
Sanders et al.	16	Every 2 yr	71.0%	Conventional	51.0%	97.0%
Kulasingam et al.	-	-	-	Conventional	55.6%[b]	95.7%[b]
Goldie et al.	ns	Every 1 yr	70.5%	Conventional[a]	66.0%	97.0%
Taira et al.	16	Every 2 yr	71.0%	Conventional	51.0%	97.0%
Elbasha et al.	ns	ns	age-specific	Liquid-based	ns	94.0%
Neilson et al.	25	Every 3 yr	80.0%	Conventional	63.0%[b]	90.0%[b]

a. Goldie et al. also report the use of liquid-based cytology for current screening (sensitivity: 84%, specificity: 88%); b. Values for CIN2+; ns: not stated; yr: year

4.2.5 Outcomes

Four of the cost-utility analyses use the same expert-based publication[94] for estimating the utility weights of the cervical cancer health states. In Elbasha et al.[87] utility weights are elicited from patients experiencing those disease states.[95] In general, there is wide variation in the reported utilities for comparable health states. For instance, the utilities for stage I cervical cancer follow-up ranged from 0.76 [87] to 0.97.[85] Another example is the quality of life of cervical cancer survivors which is estimated to be either equal to[84] or lower than (0.76[87]) that of healthy women.

4.2.6 Costs

Goldie et al.[85] adopt the widest costing perspective and incorporate indirect (time) costs in their base-case ICERs. In Neilson et al.[82] results are presented both including and excluding time costs. Since most studies include only direct medical costs, we limit our discussion of the analysis in Neilson et al. to their results without indirect costs.

4.2.7 Discounting

Following their local guidelines, annual base-case discount rates of 3% are used in the USA and 4% in Norway, for both costs and benefits. In general, the impact of the discount rate is crucial for the economic evaluation of vaccination programmes. This is because the costs of the intervention (initial HPV vaccination costs) are incurred immediately while the benefits (avoided cases and life years gained) accrue much later. Lower discount rates for both costs and benefits (or for benefits only) tend therefore to favour vaccination programmes. Despite its high influence on the studies' results, only three studies performed a sensitivity analysis on the discount rate.[84, 87, 82]

4.2.8 Modelling assumptions

Key modelling assumptions are shown in table 34.

Due to the lack of long-term data about the vaccine, the duration of protection is assumed to be either lifelong,[85, 87] or limited to 10 years.[83, 84, 86, 82] To extend the duration of vaccine protection in those latter studies, 1-dose booster shots are assumed to be administered either every 10 years,[84, 86] or only once, i.e. 10 years after initial vaccination.[82] Kulasingam et al.[83] also assess the addition of a 3-dose booster at age 22 years in their sensitivity analysis.

Two studies use an unrealistic 100% vaccination coverage.[83, 85] The results of those studies are however not expected to be sensitive to vaccination coverage assumptions, since both studies ignored herd immunity effect and did not incorporate any fixed cost (e.g. vaccination campaign…).

The reported costs of the vaccination course (3 doses of the vaccine and personnel/administration costs) have been converted by us to 2006 Euro values by the use of consumer price indexes and purchasing power parities.[96, 97] All but one study[83] use a cost for the vaccination course of ≥ €300. In Belgium, the cost of three doses of the currently marketed HPV quadrivalent vaccine is €412 (without cost for the administration of the vaccine).

Some studies assume that individuals recovering from an infection return to the susceptible state (Susceptible – Infected – Susceptible or SIS model)[84-86] while others assume that such individuals acquire type-specific immunity (Susceptible – Infected – Recovered or SIR model).[87, 82] Compared to SIS models, SIR models will provide more conservative results. Indeed, since a larger proportion of individuals are susceptible in a SIS model, the impact of vaccination will be greater in a SIS model than in a SIR model.[52] There is, however, an important lack of evidence about the true nature of the immune response and protection conferred by natural HPV infection. Therefore it is hard to assess which of the two models (if any) is most appropriate.

Table 34: Modelling assumptions

Author	Model type	SIR/SIS	Endpoints (HPV types) modelled	Cross protection	Strain replacement	Genital warts
Sanders et al.	Static	ns[a]	LR and HR[b]	No	No	No
Kulasingam et al.	Static	ns	LR and HR	No	No	No
Goldie et al.	Static	ns[a]	LR, HR 16/18 and HR non-16/18[b]	No	Yes	No
Taira et al.	Hybrid	SIS	16/18	No	No	No
Elbasha et al.	Dynamic	SIR	6/11 and 16/18	No	No	Yes
Neilson et al.	Dynamic	SIR	6/11, 16,18, and 10 other HR	No	No	No

a. Not stated but presumably a SIS model based on model schematic representation and reported assumptions; b. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are considered high-risk, all other HPV types are considered as low-risk; c. LR: low risk; HR: high risk, SIS: susceptibel-infected-susceptible; SIR: susceptible-infected-recovered

Two studies restrict their model to HPV 16/18[86] and 6/11/16/18 [87] specific (intermediate) endpoints, thereby ignoring the possibility of cross protection (i.e. the protection against strains not included in the vaccine) or strain replacement (i.e. the mechanism by which blocking some strains might allow others to flourish). The endpoints modelled by the other studies remain type-specific but include a broader range of strains. However, only Goldie et al.[85] modelled the possibility for strain replacement or mixed infections.

Only one study assessed the impact of the vaccine on the incidence of genital warts.[87] Further, none of the studies takes into account the effect of vaccination on the HPV-related non-cervical cancers, such as neck, vulva, penis and anal cancer.

Most studies did not explicitly report a comparison of the epidemiological results produced by their model (in terms on HPV infections, CIN and cervical cancers) with observed age-specific data.[83-86, 81] Such control for the face validity of their model appears to have been done in 3 studies but the results are not presented.[83, 84, 86] In Elbasha et al.[87] and Neilson et al.,[82] the model's predictions were compared with epidemiological data from national cancer registries. Both studies reported the results of this comparison (either in tables or in graphs) and stated that their predictions were generally consistent with observed data. Brisson et al.[90] takes up a different approach since their model was calibrated to adequately fit available Canadian prevalence and incidence data on HPV, genital warts, CIN and cervical cancer. Details of this procedure are reported in another publication.[98]

4.2.9 Results

4.2.9.1 Base-case results

The studies' results (standardized to Euros of the year 2006 with local consumer price indexes and purchasing power parities[96, 97]) for the various vaccination scenarios investigated are presented in table 35.

Compared with standard care, HPV vaccination of 12-year-old girls on top of the current screening programme is found to cost between €22 000 and €23 000 per QALY gained, when herd immunity effects are ignored.[84, 85] The recently published Canadian study found somewhat lower cost-effectiveness ratios: for a vaccine covering HPV 16/18 strains the incremental cost per QALY gained was estimated at almost €22 000 (80% CI: €10 618 - 38 935) and for a vaccine covering HPV 6/11/16/18 strains €14 520 (80% CI: €7 787 – 23 361).[90] As expected, the two non-static models provide more optimistic results, with ICERs ranging from €2 600 to €14 200 per QALY gained.[86, 87] The more recently published Danish dynamic model used another metric and found a cost *per life year gained* between €8 687 to €14 219, depending on the time horizon of the model.[81] Costs per QALY gained were not calculated in this Danish study. The Norwegian dynamic model reports higher ICERs: €39 400 per QALY gained.[82]

Compared to girls only, universal vaccination of all 12-year olds (girls and boys) is not considered to be cost-effective, mainly because of the high cost associated with this strategy and the small QALY gains.[86, 81, 87] Further, in Elbasha et al.[87] this scenario is

dominated (i.e. more costly and less effective) by a 12-year-old girls plus temporary female (12- to 24-years) catch-up strategy.

Girls and female catch-up vaccination appears to be cost-effective with a cost of €4 100 per QALY gained compared to girls' immunisation alone.[87] The recently published Danish model found that a catch-up vaccination programme for 13-15 year olds would be associated with a relatively high incremental effectiveness, while the additional costs are only borne in the first year. The result is a marginal increase in the incremental cost-effectiveness ratio (from approximately €8 700 to €9 000 per LYG).[81]

Adding boys and/or male catch-up vaccination, and assuming efficacy to prevent infectiousness in males, to a girls and female catch-up scenario results in better clinical effectiveness but higher ICERs (range €37 000 to €40 000 per QALY gained).[87] Similar findings resulted from the Danish model.[81]

The studies that explore the effect of optimizing the cervical cancer screening once a vaccination programme is established conclude that the age of screening initiation could be delayed without compromising efficacy. Further, increasing the interval between the screenings is found to substantially decrease the ICERs, though reducing the clinical effectiveness.[83, 85] The best balance between costs and benefits is girls' vaccination plus triennial screening starting at age 25 (€56 152 per QALY gained) in Goldie et al.[85] and girls' vaccination plus biennial screening starting at age 24 (€43 800 per LYG) in Kulasingam et al.[83] Of interest, in their sensitivity analysis, Taira et al.[86] demonstrated that the current screening strategy (71% of women screened every 2 years) was dominated by a scenario of girls vaccination combined with optimal screening (screening every 4 years).

Table 35: Results of the economic evaluations of HPV vaccination (all costs reported in € from the year 2006)

Author Costing year	Vaccination strategy	Comparator	ICER (in € 2006) € / QALY	 € / LYG
Sanders et al.				
2001 (US$)	12-yo girls + current screening practice	Current screening practice	22 203 €	31 288 €
Kulasingam et al.				
2001 (US$)	12-yo girls	No intervention	-	dominated
	Comparison with next best scenario:			
	12-yo girls + screening every 2yrs, at age 24	Screening every 3 yrs, at age 18	-	43 800 €
	12-yo girls + screening every 2yrs, at age 18	12-yo girls + screening every 2yrs, at age 24	-	90 418 €
	12-yo girls + screening every 1yr, at age 22	12-yo girls + screening every 2yrs, at age 18	-	150 489 €
	12-yo girls + screening every 1yr, at age 18	12-yo girls + screening every 1yr, at age 22	-	230 518 €
Goldie et al.				
2002 (US$)	12-yo girls + current screening practice	Current screening practice	23 325 €	-
	Comparison with next best scenario:			
	12-yo girls + screening every 5yrs, at age 30	Screening every 5 yrs, at age 25	16 510 €	-
	12-yo girls + screening every 5yrs, at age 25	12-yo girls + screening every 5yrs, at age 30	29 948 €	-
	12-yo girls + screening every 5yrs, at age 21	12-yo girls + screening every 5yrs, at age 25	55 096 €	-
	12-yo girls + screening every 3yrs, at age 25	12-yo girls + screening every 5yrs, at age 21	56 152 €	-
	12-yo girls + screening every 3yrs, at age 21	12-yo girls + screening every 3yrs, at age 25	79 669 €	-
	12-yo girls + screening every 2yrs, at age 21	12-yo girls + screening every 3yrs, at age 21	157 801 €	-
	12-yo girls + screening every 2yrs, at age 18	12-yo girls + screening every 2yrs, at age 21	268 953 €	-
Taira et al.				
2001 (US$)	12-yo girls + current screening practice	Current screening practice	14 229 €	17 370 €
	12-yo girls & boys + current screening practice	12-yo girls + current screening practice	431 313 €	521 352 €
Elbasha et al.				
2005 (US$)	12-yo girls + current screening practice	Current screening practice	2 622 €	-
	12-yo girls & boys + current screening practice	-	dominated	-
	12-yo girls + catch-up female 12-24-yo + CS	12-yo girls + current screening practice	4 127 €	-
	12-yo girls & boys + catch-up female 12-24-yo + CS	12-yo girls + catch-up female 12-24-yo + CS	36 976 €	-
	12-yo girls & boys + catch-up female & male 12-24-yo + CS	12-yo girls & boys + catch-up female 12-24-yo + CS	39 853 €	-
Neilson et al.				
2006 (NOK)	12-yo girls + CS	Current screening practice	39 392 €	47 093 €

CS: current screening practice; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality adjusted life-year; yrs: years; yo: year-old

4.2.9.2 *Sensitivity of the results*

As expected, the three static models report that their results are insensitive to the level of vaccine coverage assumed.[83-85] In the three non-static models, however, results are sensitive to vaccination coverage assumptions, especially when boys and girls vaccination is considered.[86, 87, 52] This finding was confirmed in the recently published Danish dynamic model.[81]

Only two studies assess the impact of changes in the utility weights applied to their health states.[83, 87] Both studies find their results are sensitive to such changes, with lower ICERs the more HPV disease affects quality of life. The more recently published study from Canada did not find a major impact of QoL weights on ICERs.[90]

Three studies report their results for additional discount rates: 0 and 5% in Sanders et al.[84], 1 and 5% in Elbasha et al.[87] and 3% in Neilson et al.[82] Consistently, lower discount rates for both costs and effects produce more favourable (lower) ICERs. In Elbasha et al.[87], the ICER of a girls plus temporary female catch-up vaccination scenario becomes €400 per QALY gained with a 1% discount rate and €9 000 per QALY gained with a 5% discount rate (€4 100 in the base-case). Since different national guidelines recommend different discount rates for the base-case, results should be presented over a range of discount rates to increase comparability.

Most studies find their results are fairly robust to changes in the degree of vaccine efficacy against infection.[84-87] Three studies further report that even if vaccine efficacy was reduced to 30%[86], 40%[84] or 70%[85], HPV vaccination would remain below the US threshold of $50 000 per QALY gained.

All but one study[82] find that results are sensitive to the duration of vaccine efficacy and to the need (and cost) for a booster shot. Kulasingam et al.[83] state that the administration of a booster dose at 22 years to extend efficacy duration an additional 10 years results in a cost of €75 000 per LYG (versus €43 800 in the base-case). In Sanders et al.[84] when the initial vaccination course is assumed to confer lifelong immunity, the ICER considerably improves to €12 400 / QALY gained (versus €22 200 in the base-case). Brisson et al.[90] found ICERs that were 3 to 4 times higher if vaccine protection was assumed to be 30 years instead of lifelong.

Interestingly, Neilson et al.[82] run their model for different timeframes. With a time horizon of 72 years after initial vaccination (which corresponds to lifetime) instead of 52 years, their ICER improved to €31 500 per QALY gained, compared to €39 392 in the base-case. Increasing the study time horizon therefore considerably improves the ICERs.

4.3 CONCLUSIONS

According to the studies' base-case results, and assuming that the input parameters are accurate, HPV vaccination of 12-year old girls alone appears to be cost-effective even in the setting of current screening practice. In the USA, ICERs range from €2 600[87] to €23 300[85] per QALY gained. The only European study that used QALYs as outcome is less optimistic with a cost of €39 400 per QALY gained. This result is however considered as acceptable by the Norwegian authors, especially because longer time horizons reduce the ICER.

Universal vaccination of 12-year-old boys and girls is not considered attractive, unless vaccine efficacy wanes rapidly without booster or when vaccine coverage is low.[86, 87] The addition of temporary female catch-up programme on top of girls' vaccination was found to increase clinical effectiveness at an attractive cost (€4 100 per QALY gained) in one study.[87]

One of the main shortcomings of the studies is the uncertainty around the estimates used to populate the models. There is indeed a lack of accurate information about the vaccine long-term characteristics (efficacy, cross-protection, strain-replacement), the QoL estimates and the disease epidemiology (disease progression rates, immune status conferred by a natural HPV infection). Given this broad spectrum of uncertainty, it is

surprising that none of the studies considered in the initial review performed a probabilistic sensitivity analysis. In the meantime, a probabilistic sensitivity analysis has, however, been performed in the most recent economic evaluation of Brisson et al.[90] In Elbasha et al.[87] the results of a sensitivity analysis using worst-case values for a range of critical inputs (vaccine protection duration, vaccine coverage, QoL weights and vaccine efficacy) show that the ICER of the girls plus female catch-up vaccination scenario is 6-fold higher than that of the base-case (€25 700 versus €4 100 per QALY gained). If all uncertain parameters would have been varied simultaneously (which was not done), it is therefore likely that the range of the ICERs reported for each study would be large, hampering a clear-cut judgment about the desirability of a HPV vaccination programme.

The current economic evaluations of HPV vaccination pertain mainly to the USA and Northern-Europe. Using those results in a Belgian setting should therefore be done with great caution, especially for the US findings' since health care systems and costs do not readily apply to this country.

Key points

- **The existing cost-effectiveness studies suggest that HPV vaccination of 12-year-old girls can be cost-effective, even when current screening remains unchanged.**
- **In the USA, ICERs for this strategy range from €22 200 to €23 300 (static models) and from €2 600 to €14 200 (dynamic models) per QALY gained. Canadian estimates from a static model were slightly smaller: €14 520 to €22 000 per QALY gained, depending on the type of vaccine (bivalent or quadrivalent). The ICER reported for Norway is slightly higher: €39 400 per QALY gained. A Danish dynamic model found an ICER of €8 687 per life year gained.**
- **ICERs are very dependent on the time horizon of the assessment. When the time horizon is shorter than lifelong, ICERs increase markedly.**
- **Optimisation of the current screening programme in Western countries (delayed initiation age and/or decreased screening frequency) once HPV vaccination is initiated could improve ICERs but only if future evidence about vaccine efficacy would support these strategies.**
- **Including also the vaccination of boys is generally not found to be cost-effective if a high coverage of girls is obtained.**
- **There remains great uncertainty about key input parameters. With the exception of Brisson et al., none of the studies reported the combined impact of the uncertainty for these parameters on the results.**

5 ECONOMIC EVALUATION OF HPV VACCINATION IN BELGIUM

This chapter describes an economic model for assessing the relative cost-effectiveness of HPV vaccination in Belgium in various scenarios and with different modelling assumptions. The main aim of the economic model is to assess the relative impact of different modelling assumptions on the estimate for the incremental cost-effectiveness ratio (ICER). The model does not pretend to be in itself better or to produce more accurate cost-effectiveness estimates than existing models. The analysis tries to demonstrate and evaluate the existing uncertainties associated with the modelling assumptions.

To construct an economic model on HPV vaccination, inevitably, one has to make several assumptions. As shown in the previous chapter, most existing static economic evaluation models rely on similar assumptions of the natural history of cervical cancer. However, the natural history of cervical cancer is highly uncertain (also see chapter 2). In this model, different assumptions about the natural history of cervical cancer are tested.

5.1 STUDY DESIGN

A Markov model was used to model both the cost-utility and the cost-effectiveness of HPV vaccination. The Markov model was implemented using a Multi State Life Table design (MSLT) developed in Excel,[99, 100] and using @Risk as an add-in software for probabilistic sensitivity analysis on multiple variables.[101] An incremental cost per QALY-gained (cost/QALY) and cost per life year-gained (cost/LYG) expresses the cost-effectiveness of a HPV vaccination strategy relative to screening only.

A static model was chosen for two main reasons. Most importantly, insufficient data are available for Belgium to populate a dynamic model. A dynamic model would require quite detailed information on the level of sexual activity and mixing patterns within and across age groups. It would also require a much better understanding of the natural history of HPV infection, naturally induced immunity, and the causal and temporal pathways leading ultimately to cervical cancer than is currently available. Second, the dynamic models are mainly useful to model herd immunity and/or vaccination of boys in addition to girls. With a high initial coverage of vaccination, however, herd immunity will only have a limited influence on the results of the economic evaluation. We did not consider the vaccination of boys since no evidence is currently available on the effect of HPV transmission through vaccinating males.

The analysis was performed from the perspective of the health care payer, including the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI), the Ministry of Health and the patient.

5.1.1 Model structure

The model uses a simple design, avoiding as much as possible transitions for which no or unreliable data are available. This is to limit the number of assumptions in the model.

The structure of the Markov model is presented in Figure 3. The rectangular boxes define the health states included in the model. The arrows represent the transition possibilities between states after one Markov cycle. In our model one Markov cycle corresponds to one year. Hence, it is assumed that people stay in one state for one year and can then move to another state or stay in the same state according to a given probability. The state women move to depends on the events occurring during that year. For example, women who are in the '*Susceptible*' state can either move to '*Death*', '*Complete Hysterectomy*', or '*Cervical Cancer*', depending on whether they died, have undergone a complete hysterectomy or have been diagnosed with cervical cancer respectively. The state '*Complete Hysterectomy*' refers to hysterectomy performed for

reasons other than cervical cancer in order to avoid overlap with the '*Cervical Cancer*' state.

The model structure for the screened population slightly differs from the model structure for the unscreened population because the available evidence differs for both groups. For the screened population, information exists only on the incidence of CIN 2+ lesions and not on cervical cancer, since patients in whom CIN 2+ is detected will immediately be treated and in principle no longer move to cervical cancer because of this CIN lesion. In the model, detection of a CIN 2+ lesion is not defined as a state but as an event. This means that patients in whom CIN 2+ is detected are treated in the same cycle and then go back to the state '*Susceptible*', unless the treatment consisted of a complete hysterectomy or unless they die from causes unrelated to cervical cancer. Complete hysterectomy is usually not performed only because of the CIN 2+ per se, but may be performed following CIN 2+ detection in patients in whom other indications for hysterectomy are present.

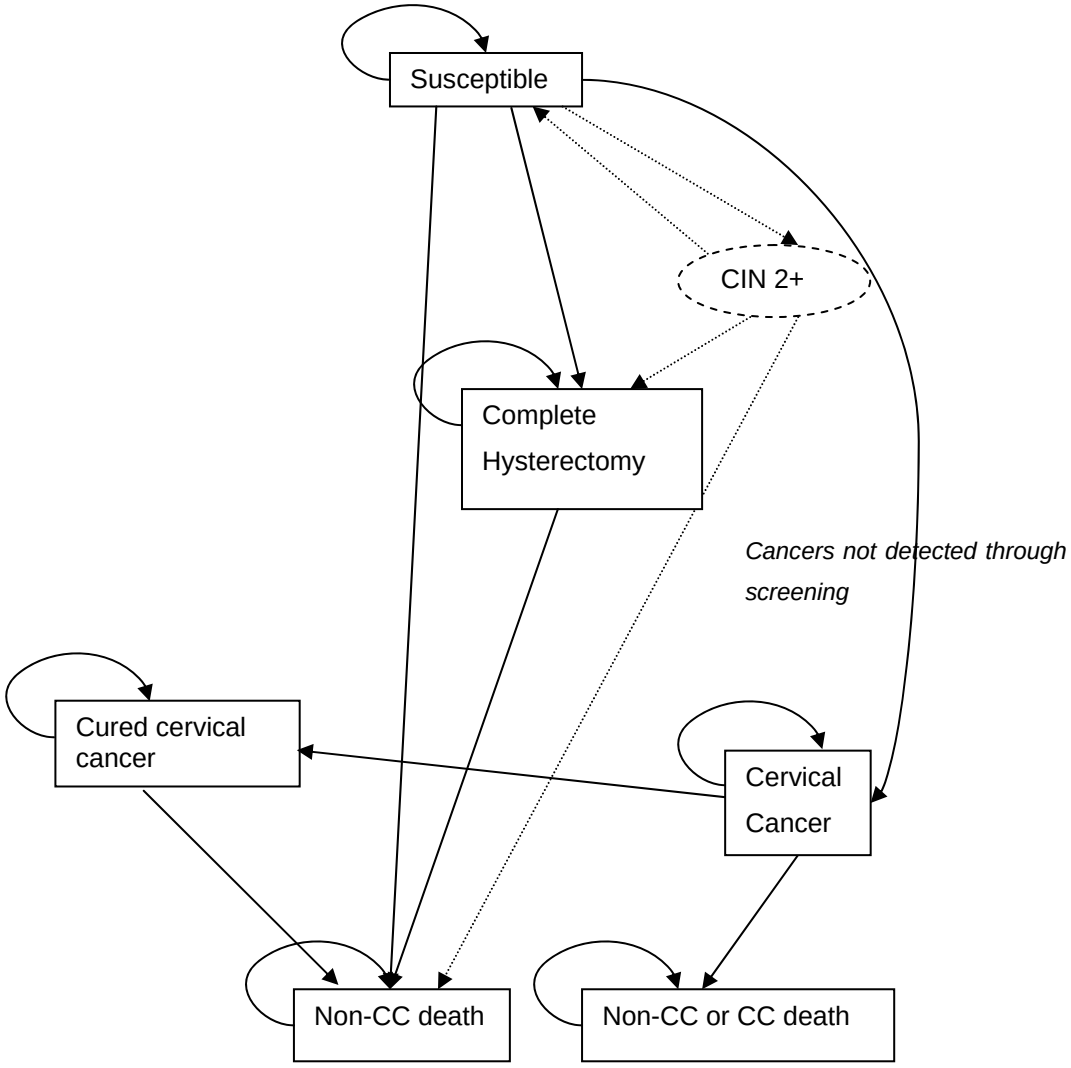
Cervical cancer screening does, however, not imply that screened women can no longer develop cervical cancer. Some forms of cervical cancers, the adenocarcinomas were, at least in the past, less affected by screening (see chapter on epidemiology). Those cancers are less frequent in natural circumstances, but due to screening their proportion has increased. In countries were screening is done, therefore, they now account for around 20% of cervical cancers diagnosed.[2] In the model we make the crude assumption that screened women are completely protected against squamous cell carcinoma but have no protection against adenocarcinoma. Therefore, the model for screened women includes both the CIN 2+-event and the '*Cervical Cancer*' state.

In the unscreened population, the non-symptomatic CIN 2+ state would not be observed. Women who are not screened therefore move directly to the state cervical cancer if they develop cervical cancer.

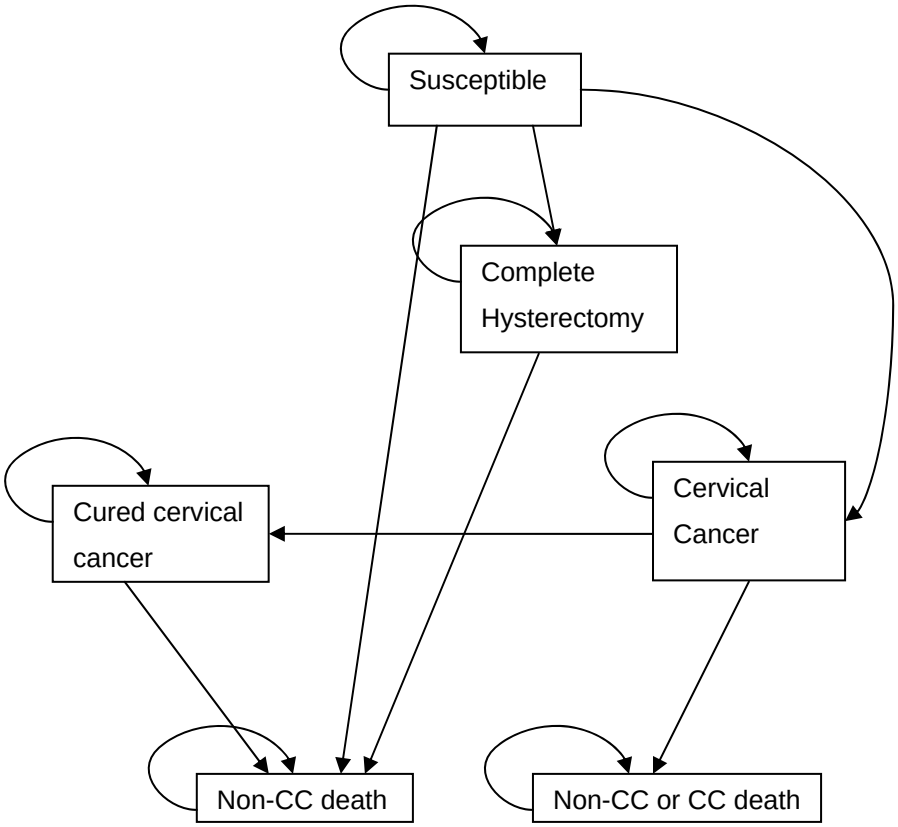
If women with cervical cancer die while being in the cervical cancer state, they will move to the '*Non-Cervical Cancer or Cervical Cancer death*' (*Non-CC or CC death*) state in our model. Hence, no distinction is made between death from cervical cancer and death from other causes since we do not exactly know the real cause of death. Women alive in the cervical cancer state are assumed to stay in this state for a maximum of 5 years. During the first 5 years after the diagnosis of cervical cancer we assume an additional mortality attributable to cervical cancer. In principle, these deaths in cervical cancer patients should be removed from the general mortality rates. However, given the small numbers of cervical cancer patients relative to the overall population, these cervical cancer-specific deaths have a very small influence on the general population mortality data. Women who survive 5 years after cervical cancer diagnosis move to the '*Cured Cervical Cancer*' state in the model.

Figure 3: Structure of the Markov model

Model structure for the screened population (with or without vaccination)



Model structure for the unscreened population (with or without vaccination)



5.2 POPULATION

The results of the model reflect the incremental cost-effectiveness of an HPV vaccination programme for a cohort of girls at a given age. In the base-case scenario we use age of 12 years for the initial vaccination and we assume unchanged screening practices. In an alternative scenario we modelled the ICER for a vaccination cohort of 16 year old girls. Vaccination of boys is not considered for reasons outlined earlier. In the model, we start with a single birth cohort of 58 958 girls. Due to general mortality, the size of the cohort becomes 58 600 at 12-years and 58 557 at 16-years of age.

5.3 EPIDEMIOLOGIC DATA

5.3.1 Mortality

Age-specific mortality rates in the general population were obtained from national statistical data for the year 2001.[102] The mortality for cured cervical cancer patients, after a 5-year survival in the cervical cancer state, was assumed to be identical to the mortality of the general population.

For cervical cancer patients, we assumed two types of mortality: (1) the age-specific mortality rate as for the general population and (2) an age-independent additional mortality rate during the first 5 years after the diagnosis of cervical cancer. The additional mortality over and above the expected age-specific general population mortality was calculated by comparing the survival of the average population with the survival of a cervical cancer population. The observed 5-year survival probability in cervical cancer patients is 68.4% according to the Flemish Cancer Registry.[3] This

corresponds to a 5-year mortality hazard rate of 0.380.[b] The expected 5-year survival probability in a general population with the same age-distribution as the cervical cancer population is obtained by weighting the age-specific 5-year survival probabilities of the general Belgian population with the number of cervical cancer cases in each age group. The weighted 5-year survival probability in those subjects is 92.6% (corresponding to a 5-year mortality hazard rate of 0.077). To obtain the observed 5-year survival probability of 68.4%, the *additional* non age-specific 5-year mortality hazard rate must be 0.303 (i.e. 0.380 - 0.077). The 1 year additional mortality hazard rate is then 0.0605 (i.e. 0.303/5).

5.3.2 Complete hysterectomy

Age-specific incidence rates for complete hysterectomy were derived from the Minimal Clinical Dataset for the year 2004 and total numbers where checked for completeness with RIZIV/INAMI reimbursement data. These data were combined with information on primary diagnosis. To estimate the transition probabilities to complete hysterectomy for other reasons than cervical cancer, hysterectomies combined with a primary diagnosis of cervical cancer or dysplasia of the cervix were excluded. The ICD-9-CM codes of excluded diagnoses are 2331, 1809, 62210, 62212, 1800, 6221, 1808, 1801. ICD-9-CM procedure codes for hysterectomy include 674, 684, 6851, 6859, 686, 687, 688, 689. Obviously, hysterectomy can only occur in women with a uterus, while the data from the Minimal Dataset and the reimbursement data are provided referring to the whole population. Therefore, the observed incidences that were measured for the whole population regardless of hysterectomy status have been recalculated to reflect the true incidence in susceptible women with a uterus, based on hysterectomy data (see further).

5.3.3 CIN 2+ lesions

The estimate of the age-specific probability of developing CIN 2+ lesions was based on data from the Minimal Clinical Dataset for the year 2004 and total numbers where checked for completeness with the reimbursement data of CIN 2+ interventions in Belgium. These interventions included conisations, cryosurgery and cauterization for destruction of a cervix lesion as well as complete hysterectomies in patients with a primary diagnosis of dysplasia of the cervix (ICD-9-CM diagnostic codes 62210, 62212 and 6221 and ICD-9-CM procedure codes 672, 6732, 6733). In the model, CIN 2+ lesions can only occur in susceptible women, i.e. without prior hysterectomy for causes other than cervical cancer. Analogously to the correction of the observed incidences of hysterectomy to incidences in women with a uterus, the incidences of CIN 2+ have been recalculated to reflect the true incidence in susceptible women with an uterus (see further). These age-specific CIN 2+ incidence rates have been applied to screened women between the ages 25- to 65-years. However, to account for the casual CIN 2+ detections outside the 25- to 65-years screening programme, age-specific CIN 2+ incidence rates have also been applied to both the screened and unscreened women aged before 25 and after 65 years.

5.3.4 Cervical cancer

Age-specific cervical cancer risk was obtained from the Belgian cancer registry.[4] These data represent the incidence of cervical cancer under current screening practices. To avoid artificial fluctuations in this age-specific incidence, numbers were averaged for the years 2001-2003. In the model, cervical cancer can only occur in susceptible women, i.e. without prior hysterectomy for causes other than cervical cancer. Again, the observed incidences have been recalculated to reflect the true incidence in susceptible women with a uterus, based on hysterectomy data (see further).

Patients with cervical cancer were assumed to move to the state 'Cervical Cancer Cured' after surviving 5 years in the state 'Cervical Cancer'.

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[b] The mortality hazard rate over 5 years is obtained by the formula : -ln(*5-year survival probability*) = -ln(0.684) = 0.3798

In 2003, the proportion of adenocarcinomas in the observed cervical cancers, under current screening circumstances, was 19.5% (data obtained directly from the Belgian Cancer Registry).

For the estimation of the risk of cervical cancer in unscreened women, information was needed on the natural history of cervical cancer. The expected incidence of cervical cancer in unscreened women was derived from an existing model for the natural history of cervical cancer.[103]

There are indications that the estimated natural incidences of cervical cancer in the model of Myers are an overestimation of the natural incidence in Belgium (Figure 4).

Figure 4A: Comparison of observed incidence (with current opportunistic screening) of cervical cancer and expected incidence without screening (natural history according to Myers).

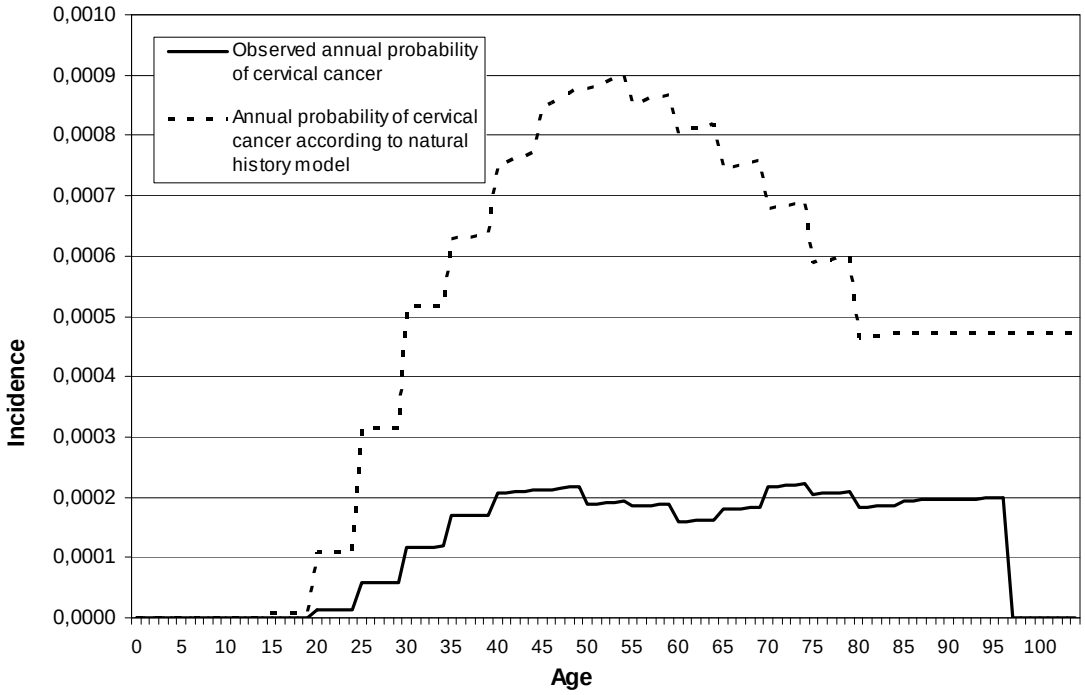
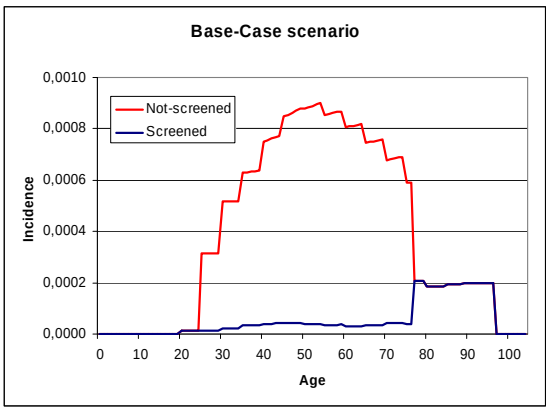
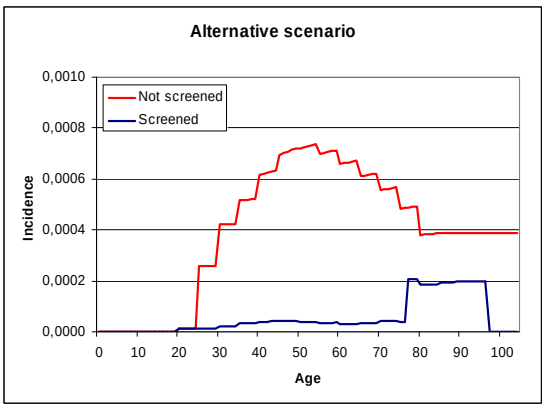


Figure 4B: Incidence selected for the model.





Previous studies have shown that screening before the age of 25 does not impact upon the cervical cancer incidence.[104, 7] Nevertheless, the difference between the observed cervical cancers in Belgium and the estimated natural incidence estimated by Myers et al.[103] is already large at this age: the natural incidence is estimated to be almost 8 times the observed incidence before the age of 25 (see Figure 4A). For the ages 25 to 65, the natural incidence is estimated to be 3.6 to 5.3 times larger than the observed incidence and after the age of 65, the natural incidence is estimated to be 2.3 to 4.1 times higher than the observed incidence.

This large discrepancy between observed and estimated natural cervical cancer incidence may influence the conclusions of our modelling exercise. For the unscreened populations, the following assumptions about the incidence of cervical cancer have been followed (see Figure 4B):

Incidence for women >65 years (both previously screened and unscreened)

After the age of 65 years, women are no longer screened. As the development of cervical cancer in previously screened women who did not have a CIN lesion at 65 takes on average 12 years in our model (see further), these women become susceptible for cervical cancer at their 77. For women of this age and older, the risk for cervical cancer should typically then be estimated from the natural history model (Myers' model). However, the fact that natural incidence (Myers' model) for women from their 77 is higher than the corresponding observed incidence in Belgium (Figure 4A) is logically incorrect. Indeed, the observed incidences relate to the entire population, including both screened and unscreened women, and as unscreened women have a higher risk for cervical cancer than screened women (if not, screening would not be effective), the risk attributed to previously screened women should never be higher than the observed risk. After the age of 77, we therefore ceiled the risk of cervical cancer in previously screened women at the observed Belgian incidence, as shown in Figure 4B.

The risk of cervical cancer for non-previously screened women older than 77 was also ceiled at the observed Belgian incidence, as for both groups there is no longer an effect of screening, so they have to be treated similarly.

For previously unscreened women aged 65 to 76 years old, since they have no protective effect on their risk for cervical cancer through the screening, their risk was estimated by the natural history model of Myers.

Incidence for unscreened women <25 years (both previously screened and unscreened)

For the group of women younger than 25 years incidences as observed in Belgium are applied to *all* women (those who are afterwards screened and those who are not).

Incidence for women aged 25 – 65 years (only unscreened)

For the unscreened women between 25 and 65 years of age, the natural history incidence (Myers') rates are used in the base-case analysis. However, given our concerns about the possible overestimation of these natural history rates, we also present an alternative scenario with lower natural incidence rates for women between 25 and 65 than the natural incidence rates predicted by the Myers model. For the estimation of the multiplicator (which must be <1) to be applied to the natural incidence rates from the Myers model, we start from the assumption that about 2/3 of the cervical cancer cases are avoided by screening.[7] If we apply currently observed incidences of cervical cancer to the cohort of 12-year olds in our model, we expect 517 cervical cancer cases. Hence, the expected number of cervical cancer cases without screening would be 1551. The corresponding multiplicator for the natural incidences presented by Myers et al. between 25 and 65 years of age is 0.82. This means that with an incidence of 0.82 times the incidences predicted by the Myers model, our model predicts 1551 cervical cancers cases if no one is screened.

Inputs in the base-case and the alternative scenario and for the different age groups and screening compliance are presented in Table 36 and illustrated in Figure 4B.

Table 36: Modelling inputs for incidence of cervical cancer in base-case and alternative scenario

	Screened	Not Screened
Base-case scenario		
< 25 years	Natural incidence ceiled at observed incidence	Natural incidence ceiled at observed incidence
25-65 years	Incidence of adenocarcinoma (19.5% of observed cervical cancers)	Natural incidence according to Myers
>65 years	65-76 years: adenocarcinoma >77years: natural incidence ceiled at observed cancer risk	65-76 years: natural incidence according to Myers >77 years: natural incidence ceiled at observed cancer risk
Alternative scenario		
< 25 years	Natural incidence ceiled at observed incidence	Natural incidence ceiled at observed incidence
25-65 years	Incidence of adenocarcinoma (19.5% of observed cervical cancers)	0.82 * natural incidence according to Myers
>65 years	65-76 years: adenocarcinoma >77years: natural incidence ceiled at observed cancer risk	0.82 * natural incidence according to Myers

5.4 INTERVENTION

5.4.1 Vaccination

The intervention consists of three doses of HPV vaccination in 12–year-old girls, added to the screening programme. Since duration of protection is currently unknown, we assume in our base-case scenario one booster vaccination 10 years after the initial vaccination. Alternative scenarios are lifelong protection or 2 boosters 10 *and* 20 years after initial vaccination.

5.4.2 Efficacy of vaccination

Vaccine efficacy is expressed in terms of protection against CIN 2+ lesions (in the population that is screened after vaccination) and protection against cervical cancer (in the population that is not screened after vaccination). This is different from most modelling studies in literature that model first the impact on HPV (specific) infections and through this intermediary state model next the impact on CIN lesions and finally cancer. The main raison for this alternative approach is that we wanted to model the impact on all CIN 2+ lesions and cervical cancers directly, and not only on those that are directly related to specific vaccine type HPV genotypes. The effect of the vaccine on genital warts and CIN 1+ was not included in the model, and neither the effect on preterm delivery as a complication of CIN treatment.

The central estimate of vaccine and booster efficacy against all CIN 2+ lesions, regardless of HPV genotype, is assumed to be 46%, with an uncertainty range of 24% to 62% (95% confidence interval) (see also the chapter on efficacy and safety) in the base-case analysis.[69] This means that as long as women are protected by the vaccine or booster against CIN 2+, their risk of CIN 2+ is 54% the risk of women not vaccinated.

Estimates for the protection against cervical cancer in unscreened women (for which no data are available) are based on the theoretical reasoning followed in multiple publications.[105, 106, 31, 98] Different models predict a larger decrease of the cervical cancer incidence than of CIN 2+ from vaccination in a sexually naive population. The theoretically assumed efficacy of the vaccine against CIN 2+ in these models is 66%[106], 49%[98] and 52.2%[31], corresponding to an assumed efficacy against cervical cancer of 76%, 61% and 68% respectively. The actual efficacy against CIN 2+ is around 46%.[69] This means that, if we apply this 46% to the relative efficacies 'predicted' by the published models, we obtain an estimated efficacy against cervical cancer of 53%, 57% or 60%. In

our base-case analysis we apply the most optimistic estimate of 60%. This estimate is also supported by the proportion of cervical cancers in Iceland reported to contain either genotype 16 or 18 but no other tested HPV type.[23]

Potential cross-protection, strain replacement or strain interaction is not explicitly considered in the model.

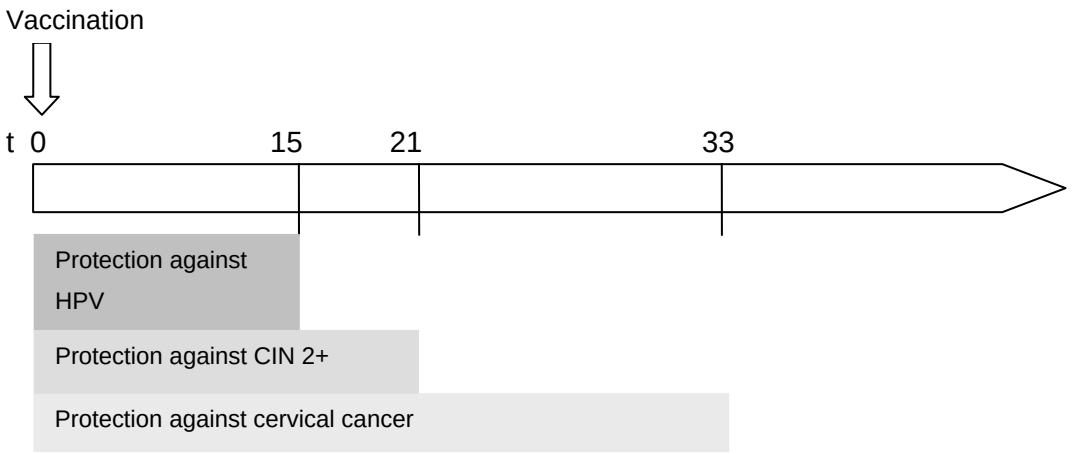
5.4.3 Duration of protection

Protection against HPV infection through vaccination is assumed to be 15 years on average (range 5-25 years). The rationale for this assumption is that with a booster at 10 years (the most frequently adopted scenario in literature if a booster is considered), the protection against HPV infection itself must be assumed longer. As mentioned before, it was found in a modelling study that HPV 16 antibody levels were predicted to remain at levels higher than after natural infection for 12 years in 50% of vaccinees or nearly life-long, depending on the model used.[77] If protection would be shorter the booster would be less effective, as some people would already get infected between the initial vaccination and the booster. An effective booster strategy should therefore be performed timely in order to avoid as many HPV infections as possible.

The *duration of protection against CIN 2+* through vaccination is even more uncertain. However, it is relatively well documented that evolution to CIN 2+ requires persistent HPV infection.[107, 18] Therefore, we assume in the base-case scenario that women are protected during six additional years against CIN 2+ lesions. This means that screened women in the model, who are no longer protected against HPV after the initial vaccination or after the last booster are still protected against CIN 2+ for an additional 6 years.

For vaccinated women who are subsequently not screened, we need an estimate of the *duration of protection against cervical cancer* through vaccination, as CIN 2+ is not included in the model for this sub-population. It is assumed that CIN 2+ lesions precede cervical cancer with at least 10 years on average. [107, 18] Based on data derived from a Dutch population-based screening program, the interval between the manifestation of the earliest lesion (CIN1) and the development of cervical cancer was estimated at about 12.7 years.[43, 44] Therefore, we assume a lag-time of 12 years between the occurrence of CIN 2+ lesions and the diagnosis of cervical cancer. The duration of extra protection against cervical cancer in vaccinated but unscreened women is thus assumed to be 18 years on average, i.e. the duration of extra protection against CIN 2+ (6 years after protection against HPV ends) *plus* the duration between CIN 2+ and the development of cervical cancer (12 years). This extra protection adds to the protection against HPV vaccination to result in a total duration of protection against cervical cancer after vaccination or booster of 15+6+12=33 years (Figure 5).

Figure 5: Duration of protection against HPV, CIN 2+ and cervical cancer after vaccination



All the point estimates for the parameters related to duration of protection or duration of evolution to CIN 2+ or cancer are included in the model with a probabilistic distribution in order to allow extensive uncertainty analysis (see paragraph 5.11).

5.4.4 Vaccine coverage

Vaccine coverage, i.e. the percentage of girls vaccinated, is assumed to be similar to the vaccine coverage for measles-mumps-rubella (MMR) in Flanders, which is given at the age of 12.[108] The documented coverage is about 84% (95% confidence interval 81.4-85.8). The authors of the report on vaccination coverage for MMR note, however, that the actual coverage may be higher, given the incomplete documentation of vaccinations.

Coverage for the booster is assumed to be significantly less, as this cannot be organised at school level but will depend more on the women's individual initiative. In the base-case analysis, booster coverage is set at 59%, which is the estimated compliance rate with three-yearly cervical cancer screening in Belgium.[7] The rationale behind this assumption is that women who regularly visit their gynaecologist will also be more likely to receive a booster dose of the vaccine when needed. In the scenario with two boosters, coverage is assumed to be the same for the second as for the first booster.

5.4.5 Screening coverage after vaccination

Screening coverage between 25 and 65 years of age after vaccination is assumed to be equal to the screening coverage equivalent (see chapter 2) without vaccination. The assumption of equal screening coverage equivalent with and without vaccination might be too optimistic, as it might be hypothesised that vaccination might give a false sense of safety and hence a reduced inclination for screening. An alternative scenario assumes a lower screening coverage in vaccinated women. There is no indication of what the level of this coverage could be. The only reason for this scenario is to assess the potential consequence of a lower screening coverage after vaccination. Therefore, we assume a coverage of 59% in this scenario, similar to the estimated current 3-yearly coverage of screening in women between 25 and 65 years of age.[7]

5.5 COMPARATOR

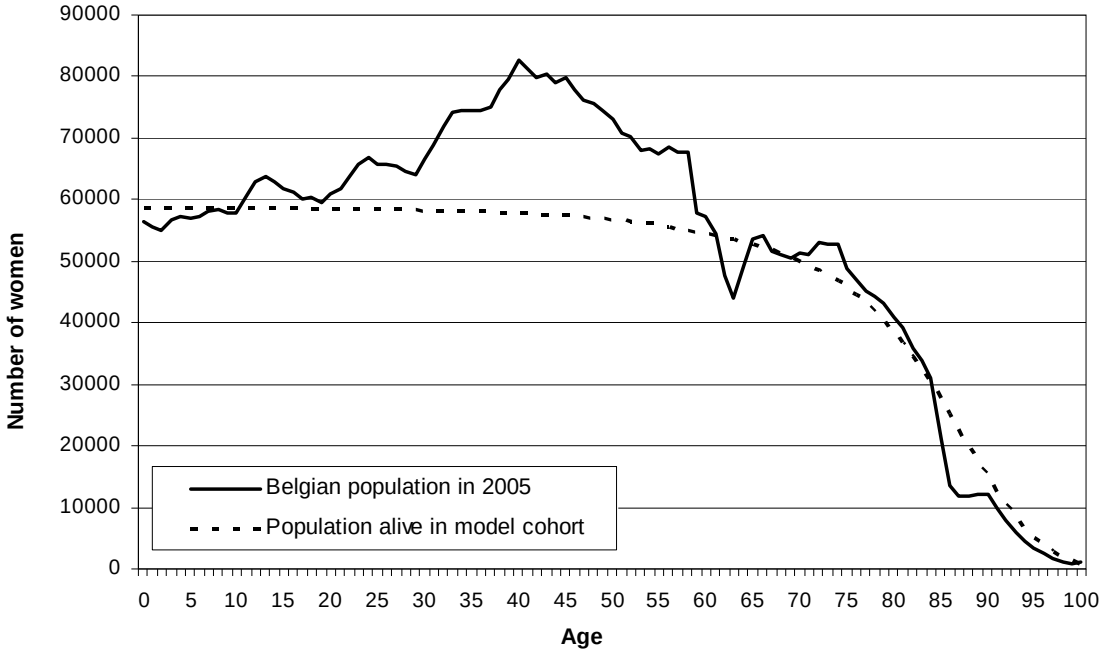
The comparator is a strategy with screening alone. The advocated optimal screening strategy in Belgium is three-yearly screening between 25 and 65 years of age,[7] but other countries have chosen different scenarios with screening intervals up to 5 years (e.g. the Netherlands).[47] It is known that there is over-screening in Belgium for a subgroup of the population, with some women being screened every year. The impact of this over-screening was however not directly modelled. On the one hand, over-screening has only a very modest impact on the benefits. If this were not the case the optimal screening strategy would need to be redefined. On the other hand, over-screening has an important impact on the costs of screening.

First, the population to which the actual expenditures apply is not identical to the population of our model. Our model follows a cohort of girls longitudinally, while the actual expenditures are generated by a cross-section of the population with a different age-structure than that of a birth cohort of women (see figure 6). Second, if current screening is relatively too expensive because of the over-screening, the first question should be how current screening practices can be optimised, both in terms of reducing the number of tests in over-screened women and in terms of increasing the participation of unscreened women. In our base-case model, we assume that the participation rate in a three-yearly screening programme remains at a level that corresponds to the number of cervical cancers currently observed (i.e. the screening coverage equivalent). If the cost thus generated by the model is less than the current budget spent on screening, there is still room for more efficient use of current screening resources. Resources could be saved by less frequent testing in screened women. Improving the participation rate, however, does not come without cost. Strategies to improve the participation with screening are beyond the scope of this report and we have therefore not considered the costs associated with screening campaigns. This precludes an economic evaluation of such 'maximal participation strategies' relative to current screening practices.

Our analysis hence pertains only to a screening programme, in a population consisting of 'compliers' and 'non-compliers' with the screening programme. The screening coverage used in our model is equal to the percentage of women screened that is needed in our model if we want to obtain the actually observed number of cervical cancer cases, given the natural incidence of cervical cancer (in non-screened women) and the observed current incidence of cervical cancer. This is the concept of 'screening coverage equivalent', already referred to in chapter 2.

The screening coverage equivalent was calculated by calibration on the expected number of cervical cancers in the model cohort without vaccination. Given the current screening situation and the currently observed age-specific incidence of cervical cancer in the Belgian population, around 517 cervical cancer cases would be expected in our model population, i.e. an annual birth cohort of 58 950 girls. This is lower than the actually observed cervical cancer incidence because the current population consists of relatively more women between 30 and 50 than in the model population (Figure 6).

Figure 6: Current population of Belgian women in 2005 versus model cohort (by age)



The model, using the natural history rates of cervical cancer as derived using the model by Myers et al.[103] from 25 years onwards predicts 1 866 cervical cancers in this same cohort without screening. If all women would be screened, 162 cervical cancers would be observed in our model; i.e. the adenocarcinoma *plus* the cervical cancers occurring before the age of 25 and after the age of 65. From this, we can derive the proportion of women that must be screened between 25 and 65 years of age to obtain 517 cervical cancers in our model cohort, i.e. the screening coverage equivalent.[c] This proportion is calculated as 79.1%.

In the *alternative scenario*, correcting the natural incidence estimates of Myers et al. [103] with a factor 0.82, an observed number of cases of 517 and a predicted number of cases without screening of 1 551 corresponds with a screening coverage equivalent of 74.3%.

Specificity of the Pap test for CIN 2+ is assumed to be 89% in the base-case analysis, based on a meta-analysis of 45 studies and with HSIL+ as the test threshold.[109, 110, 7] This figure is used for the calculation of the costs of treatment of CIN 2+. Also false positive posts will be followed-up with further diagnostic tests.

[c] coverage * 162 + (1-coverage) * 1866 = 517

5.6 OUTCOMES

Four outcome parameters are considered in the model: life years gained (LYG), Quality Adjusted Life Years (QALYs) gained, avoided cervical cancer (CC) deaths and avoided CC cases.

The number of life years gained results immediately from the model: the cumulative number of people alive at each Markov cycle in the screening strategy is subtracted from the cumulative number of people alive in each cycle in the vaccination strategy to obtain the number of life years gained with vaccination.

QALYs are obtained by weighing each year of life gained in a specific state by the quality weight of that state. For the population in the susceptible group, age-specific values from a general population study in Flanders were used.[111] Quality of life losses relative to these 'norm' values due to *CIN 2+* or due to *cervical cancer* in our model were derived from a single study, measuring the health-related quality of life of women in these states using the time trade-off approach.[112] Separate values were reported for CIN 1, CIN 2, CIN 3 and cervical cancer. Values for CIN 2 (0.809, SD 0.16) and CIN 3 (0.711, SD 0.2) were combined to obtain a single value for CIN 2+ in our model by weighing the values with their relative incidence. CIN 2 is about 65% of all CIN 2+ (see also table 11 in chapter 3), hence the weighted average value for CIN 2+ is set at 0.775. Compared to a state of perfect health (value 1 by default), this means a quality of life loss of 0.225. Relative to the population norm, the quality of life loss is 0.225 times the norm value. A similar approach is used to calculate the age-specific quality of life weights for women with cervical cancer. The quality of life value for cervical cancer was estimated to be 0.554 (SD 0.23), implying a quality of life loss of 0.446 relative to perfect health and of (0.446 * the population norm) relative to the general age-specific health related quality of life value. We assume that this is the quality of life loss for women in their first year with cervical cancer. For cured cervical cancer patients, a quality of life value of 0.84 was found in one study, implying a value loss of 0.16 relative to perfect health.[87] This is the value loss for women who survived in the *cervical cancer* state for more than five years, as after 5 years in the *cervical cancer* state, all women alive move to *cured cervical cancer*. Quality of life losses in the 2nd to 5th year in the cervical cancer state, were estimated by assuming a linear change in the quality of life loss between the first year in *cervical cancer* state and the first year in the *cervical cancer cured* state. This leads to values for Quality of Life losses of 0.389, 0.332, 0.274 and 0.217 for the second, third, fourth and fifth year in the *cervical cancer* state respectively. Each of these values is fitted with a Beta-distribution, to reflect the variation in Quality of Life values between cervical cancer patients.

5.7 COSTS

Cost items included in the model are:

- costs of initial vaccination (3 doses)
- cost of booster(s)
- cost of screening
- cost of cervical cancer treatment
- cost of CIN 2+ treatment

As the costs of hysterectomies other than for cervical cancer treatment are independent from the strategy and will therefore not have an impact on the incremental cost-effectiveness of vaccination relative to screening, these costs were not included in the analysis.

All costs are expressed for price year 2006.

The public price of one dose of the Gardasil vaccine on the Belgian market (published by the Centre Belge d'Information Pharmacothérapeutique) is €137.4 and the ex-factory price (excluding VAT and the pharmacist and distributor margins) is €120 (own computations). Further, Health Authorities could get an additional reduction (estimated

at 10%) on the ex-factory price (including VAT, €127.2) if they put a state order, hence a bulk price for one dose of the vaccine of €114.5. The cost of the initial vaccination (product costs) is thus set at €343.4. As booster vaccination cannot be organised, the cost of the booster was set at the vaccine public price (€137.4).

The first dose of the initial vaccination is assumed to be given in the context of the general vaccination programme for measles-mumps-rubella of school children at 12 years of age (despite the current absence of data that demonstrate that HPV vaccine can be given simultaneously with a MMR vaccine). Therefore, no additional administration costs are attributed to this first dose. For the second and third dose of the initial vaccination and for the booster(s) an additional administration cost of 1 GP visit per dose is added to the costs. While the second and third dose could in principle also be administered at school, this will also induce a cost. Because the costs of school vaccination programmes have not been documented yet, we conservatively assume a cost per child of 2 GP visits.

The average treatment cost of cervical cancer is based on a French study on the cost of cervical cancer treatment, as no data are available for Belgium.[113] The French study presented cost data per cervical cancer stage. On the basis of these figures, the average cost of cervical cancer treatment, weighted for the distribution of the different stages of cervical cancer in Belgium (data obtained from the Belgian Cancer Registry), a cost estimate of €16 138 was obtained. In the probabilistic sensitivity analysis, the 95% confidence intervals reported for the cost of each cervical cancer stage were used to define their probability distributions (see 6.11).

CIN 2+ is treated by conisation. The cost of a conisation procedure is €49.74. A one day hospitalisation (average cost of €126.10), one gynaecologist consultation (€20.79), an honorarium for the anaesthesiologist (€50.43) and another honorarium for post-operatory analysis of resected tissue by the anatomical pathologist (€121.44) are added to this cost. As such a total cost of €368.5 can be attributed to the treatment of CIN 2+.

The cost of screening consists of the cost of a Pap smear or LBC (€4.45 for smear taking + €19.89 honorarium anatomical pathologist), 10% re-testing is assumed, colposcopy in case of a positive Pap result (€11.06 for colposcopy + €20.79 gynaecologist consultation) and biopsy in case of visible lesions (€6.63 for biopsy taking + €53.94 for pathology). The cost of colposcopy is attributed to patients with a true or false positive Pap test result. Biopsy costs are only attributed to patients with a true positive Pap test result. A GP or gynaecologist visit cost (both €20.79) is added to the procedure costs associated with screening.

5.8 TIME HORIZON

The base-case analysis estimates the costs and outcomes of the intervention and the comparator over the lifetime of the cohort of women. The results are also presented for time horizons between 10 and 90 years, per 10 years increment.

5.9 DISCOUNTING

In the base-case analysis, costs are discounted at 3% and outcomes at 1.5%, according to the preliminary Belgian guidelines for pharmaco-economic evaluations of the KCE.[114] The following scenarios are presented: 0%, 3% or 5% for both costs and outcomes and 5% or 3% for costs and 0% for outcomes.

5.10 MODELLING ASSUMPTIONS

Due to the current absence of evidence, assumptions had to be made about the vaccine efficacy against cervical cancer, the duration of protection against HPV infection after vaccination, the natural history of cervical cancer, the coverage of the vaccine (at least for the second and third dose) and the booster(s), compliance with screening after vaccination and some of the health-related quality of life values for states included in the model (Table 37).

The rationale for the assumptions has been described in previous paragraphs. Each assumption is extensively tested in probabilistic sensitivity analyses on multiple variables.

5.11 SENSITIVITY AND SCENARIO ANALYSES

Probabilistic sensitivity analysis is performed on all input parameters that present uncertainty simultaneously. More specifically, for all variables for which data with a specified frequency distribution exist in literature, and also for all the variables for which we needed to make assumptions based on expert opinion (see also previous paragraph and Table 37) a probability distribution is defined in the model. By means of a bootstrapping technique, using @Risk software, we calculated the probability distribution for the incremental cost, outcome and cost-effectiveness ratio of vaccination relative to screening by running 1 000 Monte Carlo simulations. With each Monte Carlo simulation a random value is selected from each distribution and the results (costs, outcomes, ICERs) calculated. Based on these results, the distribution of the incremental cost-effectiveness ratio can be easily defined.

Different scenarios are presented for input variables that can take only a single specific value in the model, such as the model time span, the discount rate for costs and outcomes, the timing of the booster and the number of the boosters. Nine scenarios are presented for duration of follow-up (10 to 90, with 10 year increments) and 6 scenarios for discounting costs and outcomes, including the base-case scenario. For the boosters, a first scenario assumes one booster 10 years after initial vaccination (base-case), a second scenario assumes two boosters, one at 10 years and one at 20 years after the initial vaccination and a third assumes that no boosters are needed because the initial vaccine offers lifelong protection. In the base-case analysis, natural incidence of cervical cancer, without screening, is based on the mathematical model by Myers et al.[103]. In an alternative scenario lower incidence rates are assumed for non-screened women older than 25 years of age.

A scenario with age at vaccination set at 16 years will also be presented to estimate the incremental cost-effectiveness of a vaccination programme starting at a later age. This gives a first idea of the potential value of a catch-up programme, in the context of a population vaccination programme. With vaccination at 16 years, the vaccine efficacy will be lower. As shown in the Future II Study, vaccine efficacy against CIN 2+ is only 18% in 20 year olds.[39] Assuming a linear decrease in vaccine efficacy between 12 years of age (where we assume 46% efficacy against CIN 2+) and 20 years of age (18% efficacy), gives an estimated vaccine efficacy against CIN 2+ at 16 years of 32%. This corresponds, according to our modelling assumptions, with a vaccine efficacy against cervical cancer of 41.7%[d]. The results of this analysis give an indication of the cost-effectiveness of vaccinating older girls or women and thus the potential cost-effectiveness of a catch-up vaccination programme.

All model input parameters, with their ranges for the probabilistic sensitivity analysis or values for alternative scenarios are presented in Table 37.

[d] 46% vaccine efficacy against CIN 2+ corresponds with 60% vaccine efficacy against cervical cancer; hence 32% vaccine efficacy against CIN 2+ corresponds with 41.7% efficacy against cervical cancer.

Table 37: Modelling inputs and assumptions

	Base-case value	Scenarios	Range for probabilistic sensitivity analysis	Source
Intervention: vaccination + screening strategy				
Population (Birth cohort)	58 958 girls	-	-	
Starting age, years	12	-	-	
Time horizon	lifetime	10 to 90 yrs	-	
Vaccination coverage	83.6%	-	81.4 - 85.8	[108]
Efficacy of vaccine in reducing CIN 2+	46.0%	-	24.0 – 62.0	[69]
Efficacy in reducing cervical cancer in non-screened women	60.0%	-	Linked to vaccine efficacy against CIN 2+	Assumption, see section on efficacy and safety
Timing of booster, years after vaccination	10	10 & 20 no booster	-	Assumption
Duration of protection against HPV, after last shot of vaccination, years	15	Lifetime	5 - 25	Assumption
Duration of protection against CIN 2+, after HPV infection, years	6	-	2 - 10	Assumption
Duration of evolution to cervical cancer, given CIN 2+, years	12	-	4 - 20	Assumption
Booster coverage, % of primarily vaccinated population	59.0%	-	30 - 80	Assumption
Booster definition, number of doses	1	-	-	Assumption
Hysterectomy for other reasons than cervical cancer	age dependent	-	-	Belgian Minimal Clinical Dataset
Comparator: screening strategy				
Screening initiation age, years	25	-	-	[7]
Screening end age, years	65	-	-	[7]
Screening interval, years	3	-	-	[7]
Specificity Pap test for CIN 2+ with threshold HSIL	89.0%	-	87.0 – 90.0	[7]
False positives	11.0%	-	11.0 – 39.0	Follows from specificity
Screening coverage equivalent	79.1%	-	-	Calibrated with currently observed CC
Screening coverage equivalent after vaccination	79.1%	59.0%	-	Assumption: equal to screening coverage in screening strategy

Incidence and prevalence parameters				
Mortality according to age	age dependent	-	-	[102]
Additional annual mortality risk from cervical cancer	6.05%	-	-	Calculated
Mortality after cervical cancer cure	age-dependent mortality general population	-	-	[102]
CIN				
Annual prob of detecting CIN 2+, current screening	age dependent	-	-	Belgian Minimal Clinical Dataset
		-	-	
Cervical cancer				
Annual probability of developing cervical cancer	age dependent	-	-	[4]
Proportion of adenocarcinoma in total cervical cancers currently observed	19.5%	-	-	Belgian Cancer Registry
Treatment efficacy cervical cancer	after 5 years in state 'cervical cancer' all patients move to 'CC cured'	-	-	Assumption
Costs				
Vaccine (bulk price for 3 doses)	€ 343.4	-	-	[115]
Booster (1 dose)	€ 137.4	-	-	[115]
Administration cost initial vaccination (2 GP visits)	€ 41.5	-	-	RIZIV/INAMI reimbursement tariffs
Administration cost booster (1 GP visit)	€ 20.8	-	-	RIZIV/INAMI reimbursement tariffs
Treatment cost for cervical cancer (all stages)	€ 16 138.3	-	11 854.5 – 20 422.1	[113]
Treatment CIN 2+	€ 368.5	-	-	RIZIV/INAMI reimbursement tariffs
Colposcopy	€ 31.8	-	-	RIZIV/INAMI reimbursement tariffs
Pap test (with 10% re-test) (including GP/gynecologist consult, anatomical pathologist and smear taking)	€ 45.13	-	-	RIZIV/INAMI reimbursement tariffs
Biopsy (pathology) and biopsy taking	€ 60.6	-	-	RIZIV/INAMI reimbursement tariffs
Gynaecologist visit	€ 20.8	-	-	RIZIV/INAMI reimbursement tariffs
Quality of life weights				
Susceptible	Age-specific population norms	-		[111]

CIN 2, utility loss	0.191	-	0.177 - 0.205	[112]
CIN 3, utility loss	0.289	-	0.275 – 0.303	[112]
CIN 2+, utility loss	0.225	-	-	64% of CIN 2+ is CIN 2 (chapter 3)
Cervical cancer year 1, utility loss	0.446	-	0.430 – 0.462	[112]
Cervical cancer year 2, utility loss	0.389	-	0.372 – 0.405	[112]
Cervical cancer year 3, utility loss	0.332	-	0.315 – 0.348	[112]
Cervical cancer year 4, utility loss	0.274	-	0.258 – 0.291	[112]
Cervical cancer year 5, utility loss	0.217	-	0.201 – 0.234	[112]
Cured cervical cancer, utility loss	0.160	-	0 – 0.32	[87]
Discount rates				
Discount rate costs, %	3	0-3-5	-	[114]
Discount rate effects, %	1.5	0-3-5	-	[114]

The type and characteristics of the distributions applied to uncertain input parameters are presented in Table 38. As they are constrained on the interval zero to one, the vaccine and booster coverage rates, the specificity of the Pap test and the utility losses were all defined with Beta distributions, by means of their 95% CI or their minimum and maximum values. The treatment costs of the cervical cancer stages were fitted with normal distributions, using their reported mean and 95% CI.[113] For the efficacy of the vaccine in reducing CIN 2+, a normal distribution on the natural log (whose exponent is taken afterwards) was chosen to reflect uncertainty. To avoid extreme values, this distribution was trimmed to its 99% CI. The duration of protection conferred by the vaccine and the time to cervical cancer progression were fitted with Beta distributions by specifying their minimum and maximum values.

Table 38: Input parameters' distribution

Input parameter	*Distribution*	*Mean*	*Min*	*Max*
Vaccine coverage rate	Beta	0,836	0,814	0,858
Booster coverage rate	Beta	0,590	0,300	0,800
Duration of protection against HPV after last vaccination, years	Beta	15	5	25
Duration of protection against CIN2+ after HPV, years	Beta	6	2	10
Evolution to cervical cancer, given CIN2+, years	Beta	12	4	20
Specificity Pap test for CIN2+ with threshold HSIL	Beta	0,890	0,870	0,900
Utility loss: cured cervical cancer	Beta	0,160	0,000	0,320

Input parameter	*Distribution*	*Mean*	*2,50%*	*97,50%*
Utility loss: CIN2	Beta	0,191	0,177	0,205
Utility loss: CIN3	Beta	0,289	0,275	0,303
Utility loss: cervical cancer year 1	Beta	0,446	0,430	0,462
Utility loss: cervical cancer year 2	Beta	0,389	0,372	0,405
Utility loss: cervical cancer year 3	Beta	0,332	0,315	0,348
Utility loss: cervical cancer year 4	Beta	0,274	0,258	0,291
Utility loss: cervical cancer year 5	Beta	0,217	0,201	0,234
Treatment costs: cervical cancer stage I	Normal	9 164 €	7 052 €	11 276 €
Treatment costs: cervical cancer stage II	Normal	15 999 €	12 321 €	19 677 €
Treatment costs: cervical cancer stage III	Normal	22 697 €	15 246 €	30 148 €
Treatment costs: cervical cancer stage IV	Normal	26 886 €	21 505 €	32 267 €
Efficacy of the vaccine in reducing CIN2+	Normal on the Log	0,460	0,240	0,620

Table 39 presents a clearer overview of the assumptions in the base-case scenario and the different alternative scenarios where they differ from the base-case assumptions. For parameters that do not differ between the alternative scenario and the base-case scenario, identical central estimates and parameter distributions are applied as presented in table 37 and 38.

Table 39: Base case model and different scenarios considered

Age at vaccination	Time horizon	Number and timing of booster(s)	Duration of protection against HPV after last shot of vaccination	Screening coverage equivalent in vaccination strategy	Discount rates for costs and effects	Natural incidence of cervical cancer in non-screened between 25 and 77 years	Three-doses initial vaccination price
Base-case scenario							
12 years	Lifetime	1 booster (22 years of age)	15 years	79.1%	C: 3%, E: 1.5%	Myers' natural incidence	Bulk price: €343
Two Booster scenario							
12 years	Lifetime	2 boosters (22 and 32 years of age)	15 years	79.1%	C: 3%, E: 1.5%	Myers' natural incidence	Bulk price: €343
Lifelong protection scenario							
12 years	Lifetime	1 booster (22 years of age)	Lifelong	79.1%	C: 3%, E: 1.5%	Myers' natural incidence	Bulk price: €343
Discounting scenarios							
12 years	Lifetime	1 booster (22 years of age)	15 years	79.1%	C: 0%, E: 0% C: 3%, E: 3% C: 5%, E: 5% C: 5%, E: 0% C: 3%, E: 0%	Myers' natural incidence	Bulk price: €343
Timeframe scenarios							
12 years	10, 20, 30, 40, 50 60, 70, 80 and 90 years of follow-up	1 booster (22 years of age)	15 years	79.1%	C: 3%, E: 1.5%	Myers' natural incidence	Bulk price: €343
Reduced screening coverage after vaccination scenario							
12 years	Lifetime	1 booster (22 years of age)	15 years	59%	C: 3%, E: 1.5%	Myers' natural incidence	Bulk price: €343
Vaccination at 16 years of age scenario							
16 years	Lifetime	1 booster (26 years of age)	15 years	79.1%	C: 3%, E: 1.5%	Myers' natural incidence	Bulk price: €343
Reduced natural incidence of cervical cancer scenario							
12 years	Lifetime	1 booster (22 years of age)	15 years	74.3%	C: 3%, E: 1.5%	0.82 * Myers' natural incidence	Bulk price: €343
Vaccine price variations scenarios							
12 years	Lifetime	1 booster (22 years of age)	15 years	79.1%	C: 3%, E: 1.5%	Myers' natural incidence	From 30% to 120% of the bulk price (10% increments)

5.12 RESULTS

The effect of a vaccination strategy with one or two boosters on the number of cervical cancer cases at different ages resulting from our model is presented in Figure 7. The same data presented as cumulative number of cervical cancer cases is presented in Figure 8. The figures illustrate that even in the two boosters scenario, the number of cervical cancers avoided by vaccination remains relatively modest. Only the scenario where lifelong protection is assumed from vaccination against HPV offers a reduction of cervical cancer cases at all ages.

Figure 7: Yearly number of cervical cancer cases by age

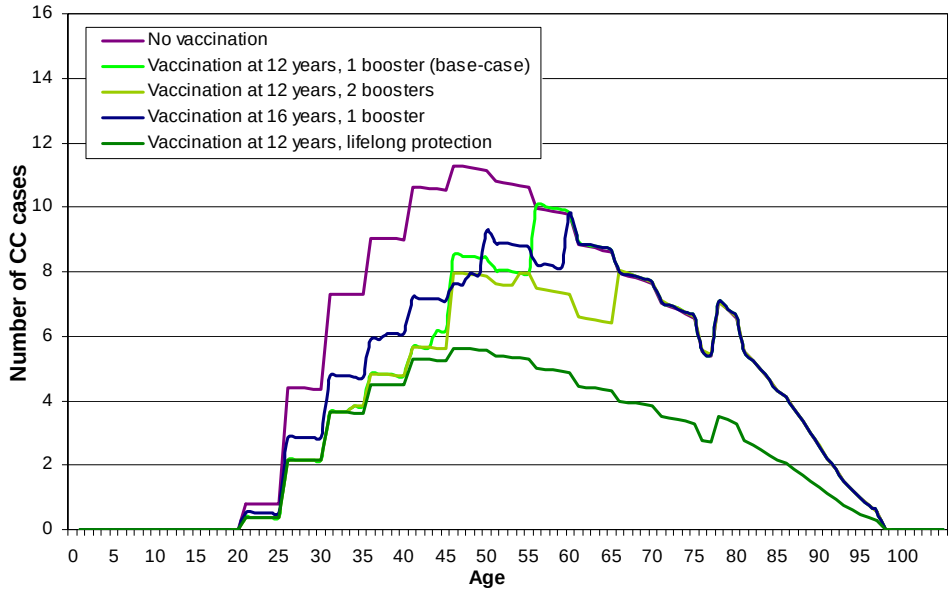
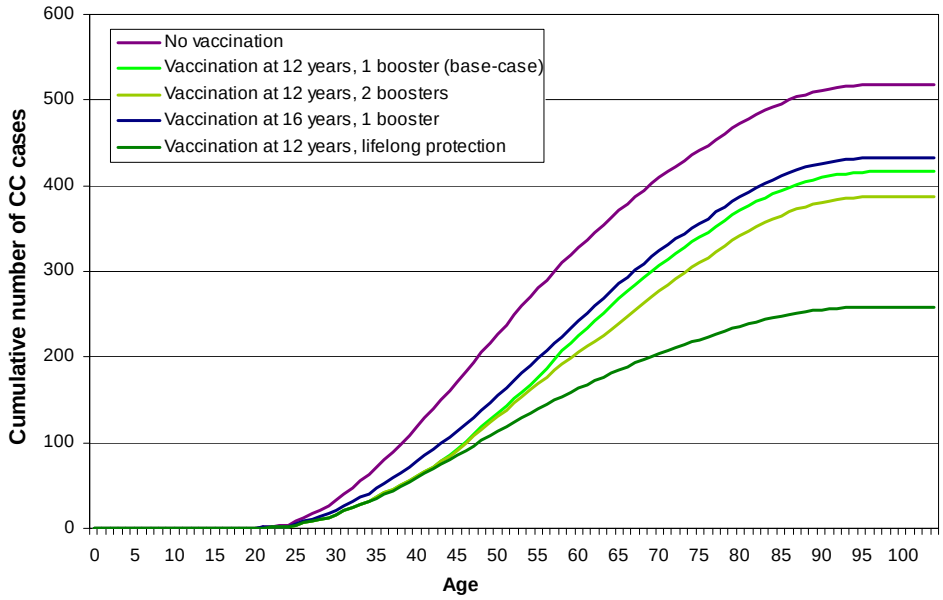


Figure 8: Cumulative number of cervical cancer cases



The individual lifetime risk of cervical cancer in the different scenarios is presented in Table 40.

Table 40: Lifetime risk of cervical cancer for 12-year olds in different scenarios

	Screened	Not screened
Not vaccinated	1 in 217	1 in 28
Vaccinated + 1 booster	1 in 232	1 in 41
Vaccinated + 2 boosters	1 in 245	1 in 50
Vaccinated + lifelong protection	1 in 556	1 in 70
Vaccinated at 16 years	1 in 230	1 in 38

To obtain the individual lifetime risk we set screening to 0 or 100% and vaccination coverage to 0 or 100% in the respective groups

The figures show the relative decline in risk for cervical cancer in different vaccination scenarios and for populations who are afterwards screened or not screened as resulting from our model.

5.12.1 Base-case results

In the absence of HPV vaccination, the base-case model predicts that of a cohort of 58 600 12-year-old girls, 519 (95% CI: 507 – 531) individuals would develop cervical cancer, which would result in 168 cervical cancer deaths (95% CI: 163 – 173). The associated (discounted) total direct medical costs is expected to reach €16 437 470 (95% CI: 16 040 060 – 16 840 540).

The addition of HPV vaccination (initial three-dose vaccination plus a booster at the age of 22) to the three-year screening programme is expected to prevent 103 (95% CI: 40 – 180) cervical cancer cases and 28 (95% CI: 11 - 49) cervical cancer deaths over the cohort's lifetime. This corresponds to a reduction of about 20% and 16% of the lifetime cervical cancer cases and deaths, respectively. HPV vaccination is further predicted to increase the cohort's life-expectancy by 1 068 undiscounted life years (95% CI: 467 – 1717) or 1 513 undiscounted quality-adjusted life years (95% CI: 630 – 2 495), which results in an average lifetime improvement of 6.7 (95% CI: 2.9 – 10.7) days or 9.4 (95% CI: 3.9 -15.5) quality-adjusted days per 12-year-old girl. In discounted values, the lifetime improvement is 3.2 days (95% CI: 1.4 – 5.0) or 5.0 quality-adjusted days (95% CI: 2.2 – 8.1). Finally, over the cohort's lifetime, the additional total costs of HPV vaccination (€18 585 470 for initial vaccination and €5 663 985 for the booster) would only be partly compensated by the reduction in CIN 2+ (€227 452) and cervical cancer (€743 444) treatment costs. The implementation of an HPV vaccination programme would require a net investment of more than €23 millions (95% CI: €22.4 – 24.0 millions) over and above the three-yearly screening costs.

Table 41: Lifetime discounted health and economic outcomes for a cohort of 58 600 12-year-old girls, Base-case

Outcomes *(95% confidence interval)*	Screening	Screening + HPV vaccination	Incremental outcome
Health outcomes (discount rate 1.5%)			
QALYs	2 127 364 *(2 126 940; 2 127 787)*	2 128 169 *(2 127 569; 2 128 704)*	806 *(348; 1 298)*
LYs	2 540 245 *(2 540 235; 2 540 252)*	2 540 756 *(2 540 472; 2 541 053)*	510 *(230; 804)*
Cervical cancers[a]	519 *(507; 531)*	416 *(333; 485)*	-103 *(-180; -40)*
Cervical cancer deaths[a]	168 *(163; 173)*	141 *(117; 160)*	-28 *(-49; -11)*
Cost outcomes (discount rate 3%)			
Initial vaccination costs	0 € *(0; 0 €)*	18 585 470 € *(18 187 090; 18 980 860 €)*	18 585 470 € *(18 187 090; 18 980 860 €)*
Booster vaccination costs	0 € *(0; 0 €)*	5 663 985 € *(5 542 529; 5 784 484 €)*	5 663 985 € *(5 542 529; 5 784 484 €)*
Screening costs	12 975 640 € *(12 901 300; 13 093 010 €)*	12 962 350 € *(12 886 160; 13 082 380 €)*	- 13 290 € *(- 21 560; - 5 183 €)*
CIN2+ treatment costs	851 416 € *(851 415; 851 416 €)*	623 964 € *(496 214; 747 582 €)*	- 227 452 € *(- 355 202; - 103 833 €)*
Cervical cancer costs	2 610 413 € *(2 221 747; 2 999 604 €)*	1 866 969 € *(1 381 172; 2 391 345 €)*	- 743 444 € *(-1 223 816; - 325 502 €)*
Total direct medical cost	16 437 470 € *(16 040 060; 16 840 540 €)*	39 702 740 € *(38 898 990; 40 580 210 €)*	23 265 270 € *(22 469 070; 24 034 440 €)*

a. Undiscounted outcome

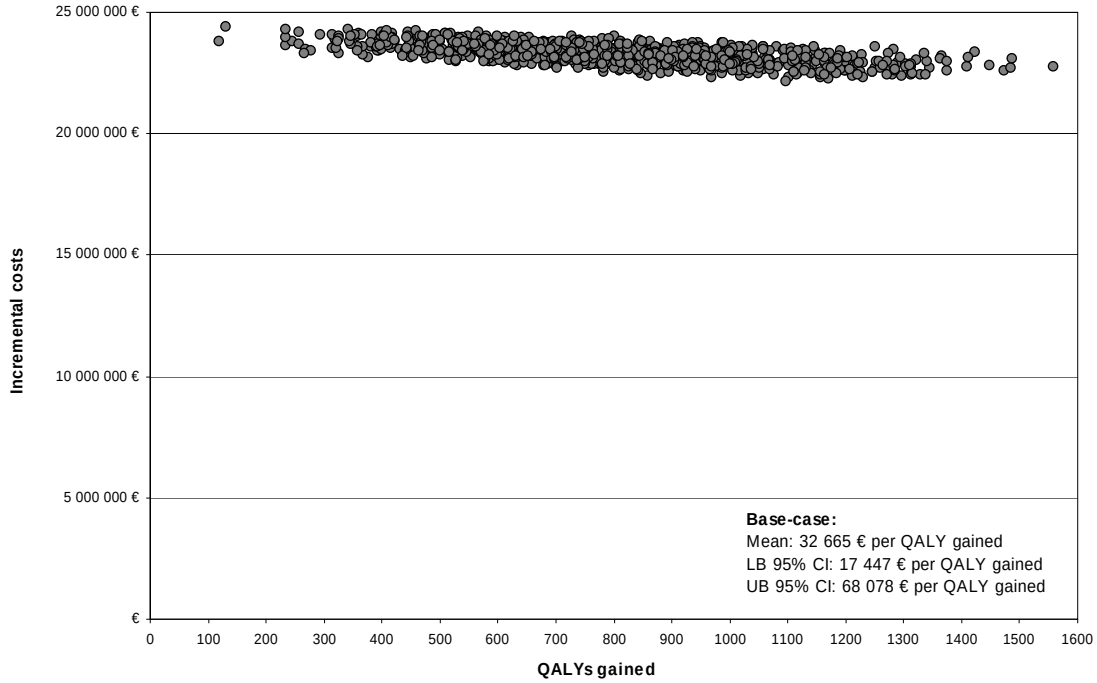
The incremental cost-effectiveness ratios in Table 42 indicate that, relative to screening alone and for the cohort's lifetime, HPV vaccination would result in an incremental cost of €32 665 (95% CI: €17 447 – 68 078) per QALY gained and €51 256 (95% CI: €28 208 – 103 147) per LYG.

Table 42: Lifetime incremental cost-effectiveness ratios of Screening + HPV vaccination versus Screening, Base-case (All costs in Euro 2006)

ICERs, Base-case	Mean	Lower bound 95% CI	Upper bound 95% CI
Cost per QALY gained	32 665 €	17 447 €	68 078 €
Cost per LY gained	51 256 €	28 208 €	103 147 €
Cost per cervical cancer averted	267 350 €	126 349 €	599 798 €
Cost per cervical cancer death averted	1 004 590 €	466 315 €	2 273 287 €

Figure 9 was obtained by plotting the probability distribution of the incremental gains (QALYs gained) against the incremental costs of the 'vaccination + screening' strategy relative to the 'screening alone' strategy, obtained from the 1000 Monte-Carlo simulations. The shape of the plot illustrates that there is much more uncertainty around the outcome-related input parameters than around the cost-related input parameters.

Figure 9: Cost-effectiveness plane, Base-case



As explained in section 6.3.4, an alternative scenario was run using a lower natural incidence of cervical cancer for unscreened women aged 25 years or older. All other assumptions were as in the base-case scenario. Reducing the natural incidence to 82% of the base-case natural incidence did not significantly impact upon the results and produced an ICER of €32 730 (95% CI: €17 492 – 67 410) per QALY gained (Tables not shown).

5.12.2 Scenario and probabilistic sensitivity analysis

5.12.2.1 'Two boosters' scenario

In the base-case, it was assumed that a booster dose would be administered 10 years after the initial vaccination course, i.e. at 22 years of age. The impact of administering a second booster dose, 20 years after the initial vaccination (i.e. at 32 years of age) is explored.

In comparison with the base-case, the 'two boosters' scenario would prevent a greater proportion of cervical cancer cases (130 cases averted or a 25.1% risk reduction) and cervical cancer deaths (35 cases averted or a 21.1% risk reduction) (Table 43). The cohort life expectancy would be higher with the administration of a second booster dose and the gain would be on average 916 discounted QALYs (i.e. 5.7 quality-adjusted days per person, 95% CI: 2.6 – 8.6) or 580 discounted life-years (3.6 days per person, 95% CI: 1.7 – 5.3).

Table 43: Lifetime discounted health and economic outcomes for a cohort of 58 600 12-year-old girls, Two boosters scenario

Outcomes *(95% confidence interval)*	Screening	Screening + HPV vaccination	Incremental outcome
Total direct medical cost	16 437 470 € *(16 040 060; 16 840 540 €)*	43 741 220 € *(42 870 320; 44 625 810 €)*	27 303 750 € *(26 401 260; 28 137 890 €)*
QALYs	2 127 364 *(2 126 940; 2 127 787)*	2 128 280 *(2 127 702; 2 128 772)*	916 *(419; 1 387)*
LYs	2 540 245 *(2 540 235; 2 540 252)*	2 540 826 *(2 540 509; 2 541 094)*	580 *(268; 849)*
Cervical cancers[a]	519 *(507; 531)*	388 *(302; 469)*	-130 *(-209; -58)*
Cervical cancer deaths[a]	168 *(163; 173)*	133 *(107; 156)*	-35 *(-58; -16)*

a. Undiscounted outcome

This improved effectiveness is however balanced by the higher cost of the strategy (net direct medical cost: €27.3 millions), so that the resulting ICERs are of the same magnitude than those for the base-case (Table 44): €32 761 (95% CI: €19 316 – 65 734) per discounted QALY gained and €51 312 (95% CI: €31 412 – 102 939) per discounted LYG.

Table 44: Lifetime incremental cost-effectiveness ratios of Screening + HPV vaccination versus Screening, Two boosters scenario (All costs in Euro 2006)

ICERs, Two boosters	Mean	Lower bound 95% CI	Upper bound 95% CI
Cost per QALY gained	32 761 €	19 316 €	65 734 €
Cost per LY gained	51 312 €	31 412 €	102 939 €
Cost per cervical cancer averted	235 343 €	127 801 €	481 283 €
Cost per cervical cancer death averted	871 400 €	460 564 €	1 786 674 €

5.12.2.2 'Lifelong protection' scenario

This scenario assumes that the initial 3-doses vaccination course confers lifelong protection to the beneficiaries, so that boosters are no longer needed. The 'lifelong protection' scenario results in the greatest clinical effectiveness since it prevents 49.3% of the cervical cancer cases (256 cases, 95% CI: 140 - 347) and cervical cancer deaths (83 cervical cancer deaths, 95% CI: 45 – 113) occurring in the cohort (Table 45). Over the cohort lifetime, 793 (95% CI: 432 – 1 071) discounted LYs and 1 262 (95% CI: 677 – 1 776) discounted QALYs would be gained. This represents a gain of 4.9 (95% CI: 2.7 – 6.7) days or 7.9 (95% CI: 4.2 -11.1) quality-adjusted days per 12-year-old girl. The incremental cost of HPV vaccination assuming lifelong protection would reach €17 millions (95% CI: €16.1 – 17.7 millions).

Table 45: Lifetime discounted health and economic outcomes for a cohort of 58 600 12-year-old girls, Lifelong protection scenario

Outcomes *(95% confidence interval)*	Screening	Screening + HPV vaccination	Incremental outcome
Total direct medical cost	16 437 470 € *(16 040 060; 16 840 540 €)*	33 391 980 € *(32 656 640; 34 266 600 €)*	16 954 520 € *(16 179 230; 17 757 300 €)*
QALYs	2 127 364 *(2 126 940; 2 127 787)*	2 128 626 *(2 127 997; 2 129 099)*	1 262 *(677; 1 776)*
LYs	2 540 245 *(2 540 235; 2 540 252)*	2 541 038 *(2 540 680; 2 541 317)*	793 *(432; 1071)*
Cervical cancers[a]	519 *(507; 531)*	263 *(172; 378)*	-256 *(-347; -140)*
Cervical cancer deaths[a]	168 *(163; 173)*	85 *(56; 122)*	-83 *(-113; -45)*

a. Undiscounted outcome

The ICERs associated with the 'lifelong protection' scenario are the most favourable with an incremental cost of €14 382 (95% CI: €9 238 – 25 644) per discounted QALY gained and €22 663 (95% CI: €15 177 – 40 390) per discounted LYG (Table 46).

Table 46: Lifetime incremental cost-effectiveness ratios of Screening + HPV vaccination versus Screening, Lifelong protection scenario (All costs in Euro 2006)

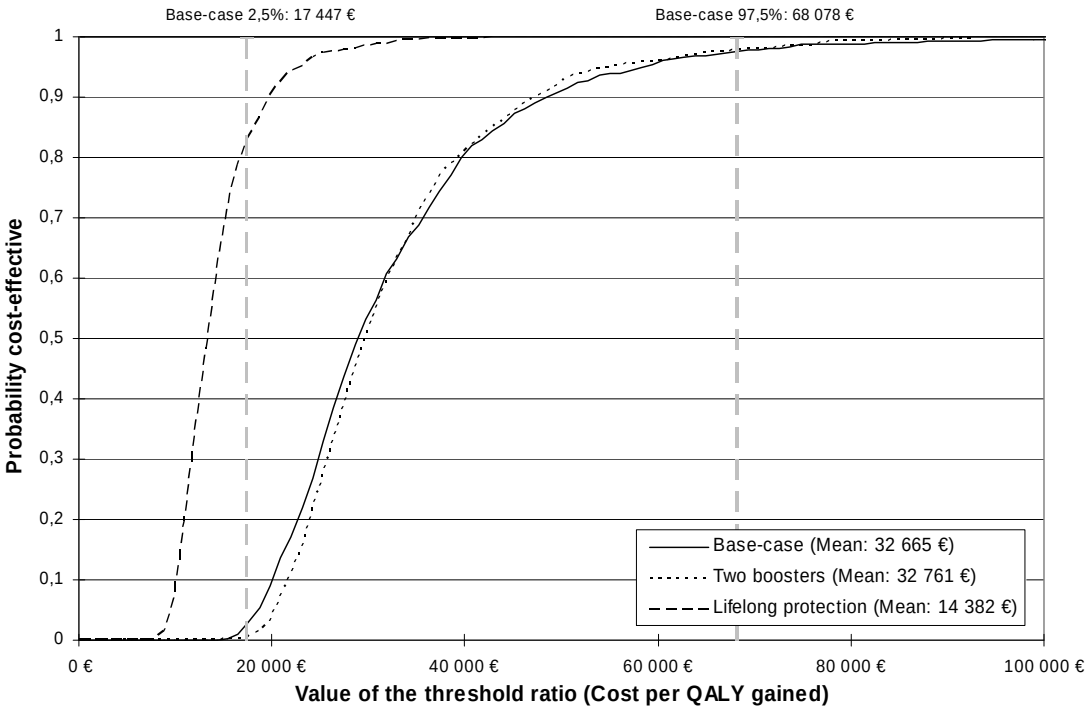
ICERs, Lifelong protection	Mean	Lower bound 95% CI	Upper bound 95% CI
Cost per QALY gained	14 382 €	9 238 €	25 644 €
Cost per LY gained	22 663 €	15 177 €	40 390 €
Cost per cervical cancer averted	70 303 €	47 083 €	126 058 €
Cost per cervical cancer death averted	216 896 €	144 858 €	390 986 €

Figure 10 presents the cost-effectiveness acceptability curves for the base-case and the 'two-boosters' and 'lifelong protection' scenarios. The curves represent, for each scenario, the probability that HPV vaccination is cost-effective for various threshold values of the cost per QALY gained. The mean ICERs of the three scenarios are reported, together with the 95% CI for the base-case.

None of the curves cuts the vertical axis, showing that HPV vaccination under the perspective of the health care payers is never cost-saving. The curve to the left of the graph represents the most favourable scenario of vaccine lifelong protection. Under this scenario, the probability that the ICER is below €20 000 per QALY is 90.7% and the probability that the ICER is above €30 000 per QALY is almost nil (1.4%).

The cost-effectiveness acceptability curves for the base-case and 'two boosters' scenario are rather similar. With a threshold of €30 000 per QALY, the probability that HPV vaccination is cost-effective is 54.0% for the base-case and 51.7% for the 'two boosters' scenario. With a threshold of €45 000 per QALY, the probability that HPV vaccination is cost-effective is around 87% for both scenarios.

Figure 10: Cost-effectiveness acceptability curves for the base-case, two-boosters and lifelong protection scenarios



5.12.2.3 Discounting scenarios

The impact of the discount rate on the base-case results was investigated by applying the same discount rates (0%, 3% and 5%) to both the costs and outcomes. Results are also presented with outcomes undiscounted and costs discounted at 3% and 5%. The costs of the HPV vaccination programme being incurred in the short term (initial vaccination costs at time 0 and the costs of the booster 10 years later), the ICERs are rather insensitive to variations in the discount rate for costs. With effects undiscounted, the ICERs ranged indeed from €16 952 per QALY gained (with a 5% discount rate for costs) to €17 627 per QALY gained (with a 0% discount rate for costs).

By contrast, varying the discount rate for effects has a strong impact on the results, with more favourable (lower) ICERs for lower discount rates for effects (Table 47). With both costs and effects discounted at a 3% discount rate, as typically done in economic evaluations of HPV vaccination described in literature (cf chapter 4), the incremental cost of HPV vaccination was €56 149 (95% CI: 31 213 – 114 326) per QALY gained or €100 213 (95% CI: 56 489 – 198 020) per LYG. ICERs generated by our model, with our modelling assumptions but with a 3% discount rate for costs and effects, are higher than ICERs presented in literature.

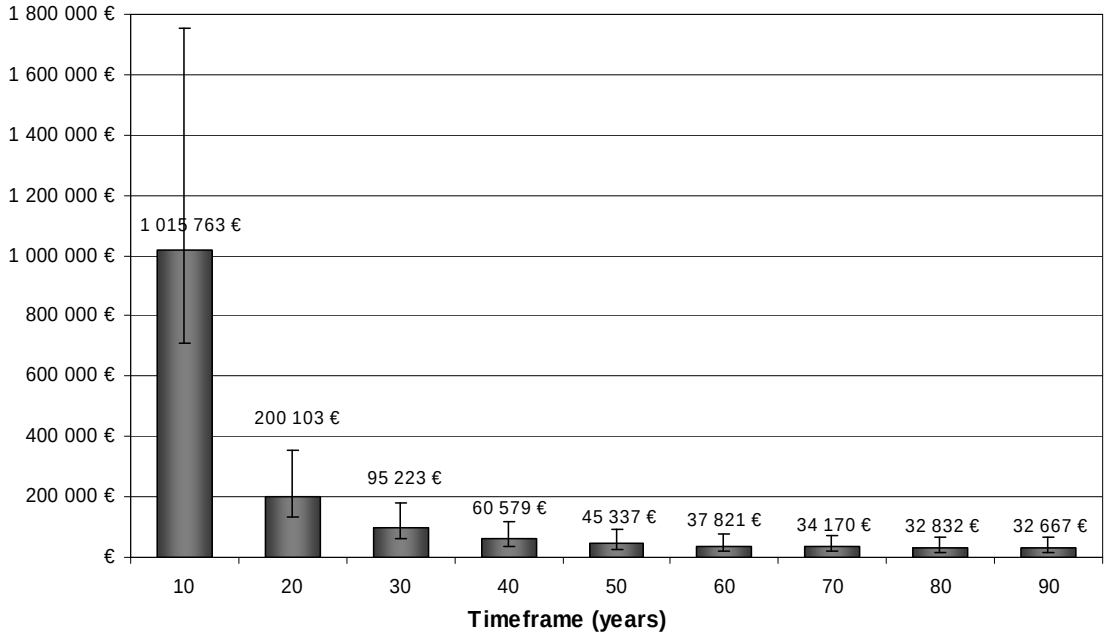
Table 47: Impact of the discount rate on the incremental cost-effectiveness ratios (All costs in Euro 2006)

Discounting scenarios	Mean	Lower bound 95% CI	Upper bound 95% CI
Cost per QALY gained			
Base-case (Costs: 3%; Effects: 1,5%)	32 665 €	17 447 €	68 078 €
Costs: 0% Effects: 0%	18 672 €	9 275 €	40 871 €
Costs: 3% Effects: 3%	56 149 €	31 213 €	114 326 €
Costs: 5% Effects: 5%	100 406 €	59 116 €	193 992 €
Costs: 5% Effects: 0%	16 952 €	8 818 €	36 319 €
Costs: 3% Effects: 0%	17 627 €	9 079 €	38 010 €
Cost per LY gained			
Base-case (Costs: 3%; Effects: 1,5%)	51 256 €	28 208 €	68 078 €
Costs: 0% Effects: 0%	26 216 €	13 370 €	54 564 €
Costs: 3% Effects: 3%	100 213 €	56 489 €	198 020 €
Costs: 5% Effects: 5%	217 247 €	129 550 €	424 185 €
Costs: 5% Effects: 0%	23 797 €	12 889 €	48 236 €
Costs: 3% Effects: 0%	24 746 €	13 233 €	50 491 €

5.12.2.4 Timeframe scenario

The base-case scenario takes into account all the HPV-related costs and benefits occurring during the cohort's lifetime. The impact on the base-case ICERs of using shorter time horizons is now explored, by varying the timeframe between 10 and 90 years (10-year increments). As expected, shorter time horizons produced higher ICERs with a cost per QALY just over €1 million within a 10-year timeframe. Since the benefits of HPV vaccination (i.e. reduction in cervical cancer cases and cervical cancer deaths) start years after the initial vaccination and spread out over a long period of time, using longer timeframes considerably decreased the ICERs (Figure 11). This decrease is however not linear.

Figure 11: Evolution of the ICER (cost per QALY gained) over different time horizons, Base-case (All costs in Euro 2006)



5.12.2.5 Reduced screening coverage with HPV vaccination

In the base-case, it was assumed that the screening coverage equivalent once HPV vaccination is implemented remains unchanged, at a rate of 79.1%. It may be argued however that HPV vaccination could induce a false sense of security, thereby reducing the compliance with screening. The current scenario explores the impact on the ICERs of reducing the screening coverage equivalent of the 'HPV vaccination + screening' strategy to 59%, while keeping it at 79.1% in the 'screening alone' strategy.

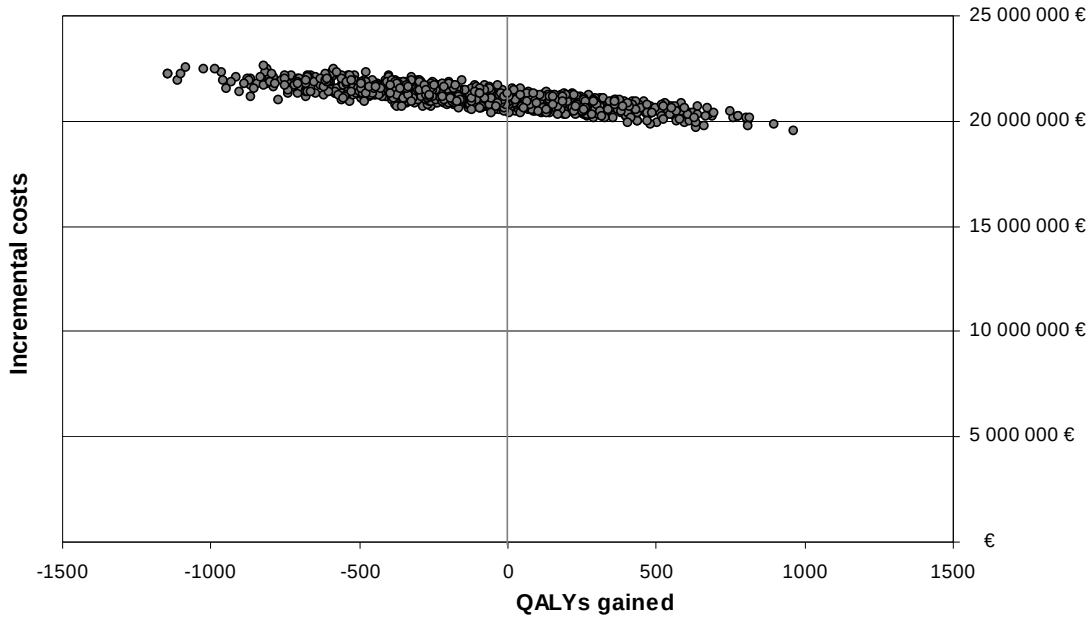
As illustrated in Table 48, if HPV vaccination has a deleterious effect on the screening compliance rate, HPV vaccination should not be recommended since it costs more than screening alone (€21 098 450, 95% CI: €20 142 020 – 22 123 550) and results in an increase in cervical cancer cases (149 cases, 95% CI: 18 - 256) and deaths (45 deaths, 95% CI: 11 – 74). This strengthens the importance of keeping the screening compliance high if an HPV vaccination programme is introduced. Note that the screening coverage in the post-vaccination period should at least reach 71%, for the benefits of HPV vaccination to compensate the damage caused by the reduced screening coverage (in terms of cervical cancer cases).

Table 48: Lifetime discounted health and economic outcomes for a cohort of 58 600 12-year-old girls, Scenario assuming a reduced screening coverage once HPV vaccination is initiated

Outcomes *(95% confidence interval)*	Screening	Screening + HPV vaccination	Incremental outcome
Total direct medical cost	16 437 470 € *(16 040 060; 16 840 540 €)*	37 535 920 € *(36 510 220; 38 701 530 €)*	21 098 450 € *(20 142 020; 22 123 550 €)*
QALYs	2 127 364 *(2 126 940; 2 127 787)*	2 127 262 *(2 126 309; 2 128 091)*	-101 *(-824; 616)*
LYs	2 540 245 *(2 540 235; 2 540 252)*	2 539 975 *(2 539 462; 2 540 477)*	-270 *(-779; 238)*
Cervical cancers	519 *(507; 531)*	668 *(533; 777)*	149 *(18; 256)*
Cervical cancer deaths	168 *(163; 173)*	214 *(177; 243)*	45 *(11; 74)*

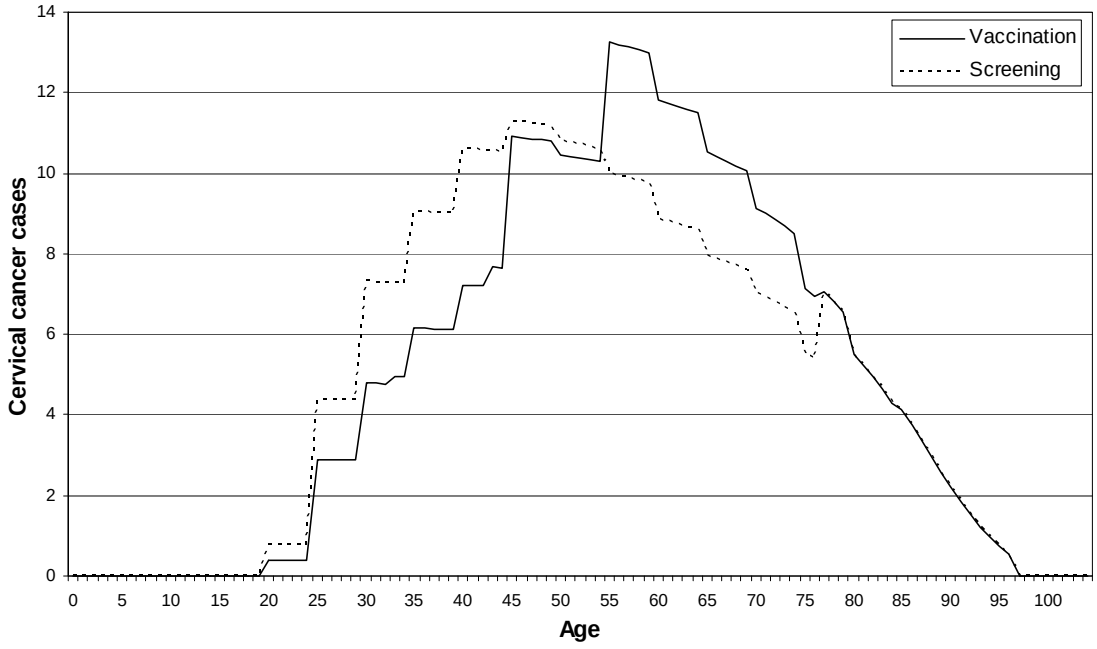
A reduced screening coverage after HPV vaccination implementation would further result in a loss of 101 discounted QALYs or 270 discounted LYs. Given the high uncertainty associated with those two parameters, their 95% CIs are wide and include the value 0 (95% CI: – 824 to 616 for QALY gained and -779 to 238 for LYG). When plotted on the cost-effectiveness plane (Figure 12), the dots representing the joint distribution of the incremental costs and effects are thus not only located in the north-east quadrant (i.e. intervention more effective and more costly) but also in the north-west quadrant (i.e. intervention less effective and more costly), which prevents the computation of a mean ICER and its 95% CI. About 63% of the dots are situated in the north-west quadrant. There is thus a 63% likelihood that HPV vaccination with reduced screening compliance would be dominated by the strategy 'screening alone'.

Figure 12: Cost-effectiveness plane, Reduced screening coverage with HPV vaccination



A threshold analysis on the point estimate of the number of cases avoided by a vaccination strategy showed that at a screening coverage rate of 71% after vaccination, no cases of cervical cancer would be avoided in the base case scenario (1 booster). Figure 13 shows the number of cervical cancer cases avoided per age in case the screening coverage after vaccination decreases to 71%.

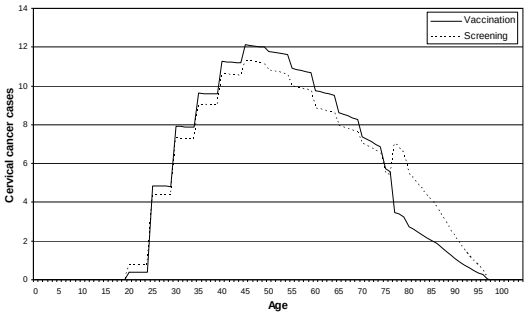
Figure 13: Cervical cancer cases in the vaccination and screening strategy, given a screening coverage after vaccination of 71% (base-case scenario)



In an optimistic scenario where lifelong protection against HPV is assumed, no cervical cancer cases are avoided with vaccination if the screening coverage after vaccination decreases to 49% (Figure 14). Moreover, in this scenario the cervical cancer cases avoided occur mainly in the older age groups while more cervical cancer cases occur at younger ages. This is due to our assumption that after the age of 77 the effect of screening is absent, but assuming lifelong protection against HPV, an effect on cervical cancer would still be observed after the age of 77. Trial and error runs of the model showed that with a screening coverage after vaccination of about 53%, we could avoid those additional cancer cases up to the age of 70 and after this age, slightly less cervical cancer cases would occur in the vaccination strategy (Figure 14).

Figure 14: Cervical cancer cases in the vaccination and screening strategy, given lifelong protection against HPV infection, and

49% screening coverage after vaccination



53% screening coverage after vaccination

5.12.2.6 Vaccination at age 16

As an indication for the potential value of a catch-up vaccination programme, a scenario with vaccination age sets at 16 years is presented.

In the absence of vaccination, the model predicts that for each 16-year-old girls' cohort, 519 cervical cancer cases (95% CI: 507 – 531) and 168 cervical cancer deaths (95% CI: 163 - 173) would occur (Table 49). Those values are the same as for the base-case which indicates that cervical cancer cases and deaths are not expected to arise between 12 and 16 years of age. As they are older than for the base-case, the mean survival of the 16-year-old cohort in terms of discounted LY (2 452 862) or discounted QALYs (2 014 647) is lower than that of the base-case.

Because the model assumed a less effective vaccine when administered at older ages, HPV vaccination of 16-year-old girls is predicted to avert less cervical cancer cases (84 cases, 95% CI: 21 – 154, or 16.1%) and deaths (23 deaths, 95% CI: 5 – 42, or 13.4%) compared to the base-case. Similarly, the cohort's life expectancy is expected to increase by 418 discounted LY (2.6 days per person, 95% CI: 0.7 – 4.5) and 660 discounted QALYs (4.1 quality-adjusted days per person, 95% CI: 1.0 – 7.3), a slightly lower improvement compared to 12-year-old vaccination. Further, 16-year-old HPV vaccination would avert less CIN 2+ and cervical cancer treatment costs, and would result in a net cost of €23 365 640 (95% CI: €22 549 240 – 24 196 770).

Table 49: Lifetime discounted health and economic outcomes for a cohort of 58 557 16-year-old girls

Outcomes *(95% confidence interval)*	Screening	Screening + HPV vaccination	Incremental outcome
Health outcomes (discount rate 1.5%)			
QALYs	2 014 647 *(2 014 202; 2 015 089)*	2 015 307 *(2 014 665; 2 015 894)*	660 *(166; 1 164)*
LYs	2 452 862 *(2 452 851; 2 452 869)*	2 453 281 *(2 452 964; 2 453 581)*	418 *(107; 721)*
Cervical cancers[a]	519 *(507; 531)*	435 *(360; 501)*	-84 *(-154; -21)*
Cervical cancer deaths[a]	168 *(163; 173)*	146 *(125; 164)*	-23 *(-42; -5)*
Cost outcomes (discount rate 3%)			
Initial vaccination costs	0 € *(0; 0 €)*	18 571 070 € *(18 173 590; 18 965 810 €)*	18 571 070 € *(18 173 590; 18 965 810 €)*
Booster vaccination costs	0 € *(0; 0 €)*	5 654 185 € *(5 533 054; 5 774 664 €)*	5 654 185 € *(5 533 054; 5 774 664 €)*
Screening costs	14 604 200 € *(14 520 580; 14 736 660 €)*	14 592 320 € *(14 507 800; 14 724 100 €)*	- 11 878 € *(- 20 098; - 3 200 €)*
CIN2+ treatment costs	955 341 € *(955 340; 955 341 €)*	758 664 € *(628 038; 899 559 €)*	- 196 677 € *(- 327 301; - 55 782 €)*
Cervical cancer costs	2 938 108 € *(2 502 977; 3 376 437 €)*	2 287 042 € *(1 719 537; 2 869 098 €)*	- 651 066 € *(-1 168 034; - 173 669 €)*
Total direct medical cost	18 497 650 € *(18 040 580; 18 951 770 €)*	41 863 290 € *(41 004 090; 42 757 500 €)*	23 365 640 € *(22 549 240; 24 196 770 €)*

a. Undiscounted outcome

The incremental cost-effectiveness ratios presented in Table 50 show that 16-year-old vaccination is less cost-effective than 12-year-old vaccination and is associated with a costs of €45 020 (95% CI: €19 601 – 138 434) per discounted QALY gained or €70 994 (95% CI: €31 779 – 223 679) per discounted LYG.

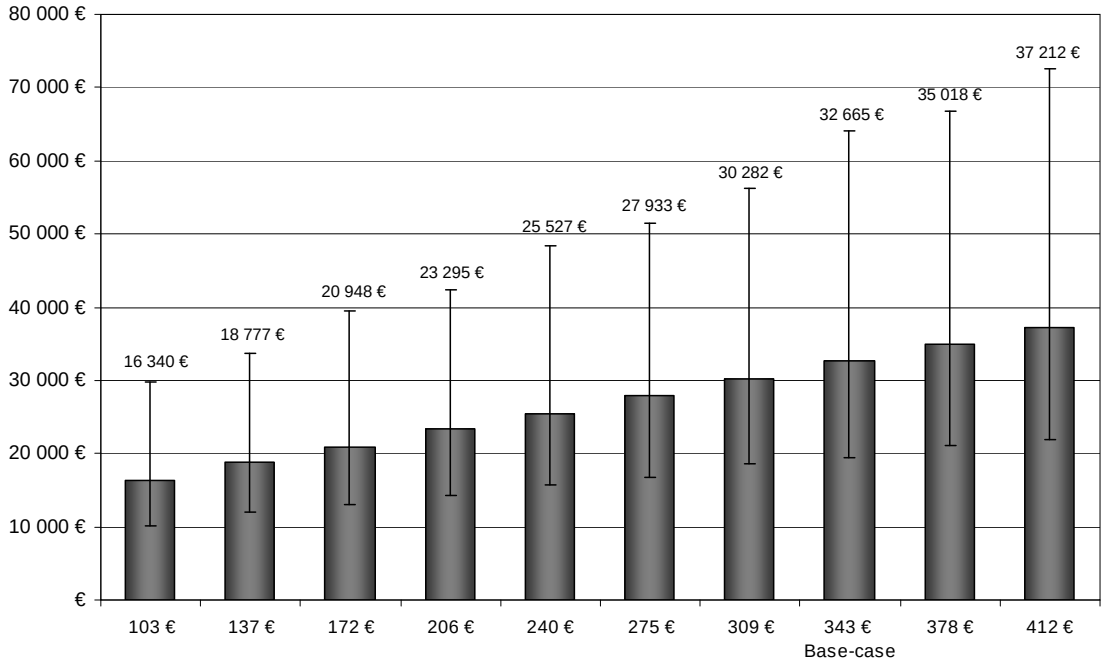
Table 50: Lifetime incremental cost-effectiveness ratios of Screening + HPV vaccination versus Screening, 16-year-old girls vaccination (All costs in Euro 2006)

ICERs, Base-case	Mean	Lower bound 95% CI	Upper bound 95% CI
Cost per QALY gained	45 020 €	19 601 €	138 434 €
Cost per LY gained	70 994 €	31 779 €	223 679 €
Cost per cervical cancer averted	366 332 €	147 458 €	1 169 164 €
Cost per cervical cancer death averted	1 368 337 €	544 366 €	4 379 926 €

5.12.2.7 Vaccine price variations scenario

In the base-case scenario, the initial 3-dose vaccination is set at the price of €343.4 (bulk price per dose: €114.5). In this scenario, we explore the impact on the base-case ICER of using different prices for the initial 3-course vaccination. The price is varied between 30% of the base-case price (€103 for the complete course or €34.3 per dose) and 120% of this price (with 10% increments), which corresponds to the public vaccine price of €137.4 per dose.

Figure 15: Evolution of the ICER (cost per QALY gained) for different prices of the vaccine (from 30% to 120% of the 3-doses bulk price), Base-case scenario (all costs in Euro 2006)

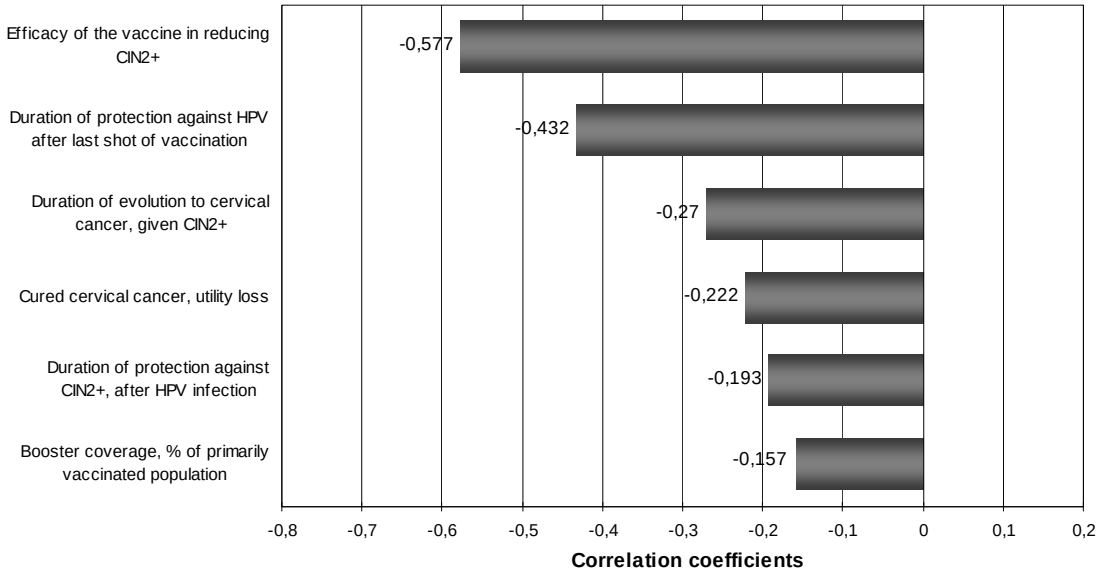


As expected, higher vaccination prices produced higher ICERs. When the public price of the vaccine is used (€412 for the vaccination course), the ICER reaches indeed €37 212 per QALY gained (95% CI: €19 645 - €78 351). For the mean ICER to be below €20 000 per QALY, the price of the initial 3-dose vaccination should be more than halved: the ICER is €20 948 per QALY gained (95% CI: €11 165 - €43 872) with a price of €172 for 3 doses.

5.12.2.8 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are presented in Figure 16. This graph shows which parameters contribute most to the uncertainty around the expected base-case ICER (€32 665 per QALY gained, 95% CI: €17 447 – 68 078). Only input parameters whose coefficient exceeds 0.1 in absolute value are plotted. Not surprisingly, the parameters with the greatest impact on the base-case ICER are all related to the vaccine effectiveness. They are thus all negatively correlated with the ICER: a higher vaccine effectiveness being associated with a lower (better) ICER. The most influential input parameters were the efficacy of the vaccine in reducing CIN 2+ lesions and the duration of protection against HPV infection conferred by the vaccine. The extra duration of protection against cervical cancer and the utility loss of one year spent in the cured cancer state were also important parameters in terms of explaining the variations around the ICER.

Figure 16: Probabilistic sensitivity analysis for the base-case ICER (cost per QALY gained) after 1000 Monte-Carlo simulations



5.12.3 Budget impact analysis

The yearly impact on the health care budget of starting an HPV vaccination programme versus the three-yearly screening was investigated, and the results are presented in Figure 17 and Figure 18.

For this budget impact analysis, only the direct costs of medical care are considered from the perspective of the RIZIV / INAMI and Ministry of Health, excluding patients' out-of-pocket payments, and costs were not discounted. All other assumptions were as for the base-case cost-effectiveness analysis.

Figure 17 presents the total yearly budget consumed if HPV vaccination of 12-year-old girls starts in 2007 and is carried on each subsequent year. The graph shows the evolution of the vaccination and booster costs, as well as the evolution of the screening, CIN 2+ and cervical cancer treatment costs over years. After the start of HPV vaccination in 2007, each new cohort of 12-year-old girls would be vaccinated, which represents an annual cost of €18 487 860 (95% CI: €18 091 570 – 18 881 170) assuming a constant cohort size of 58 600 adolescent girls. Ten years after the start of the vaccination programme, from 2017 onwards, each new cohort of 22-year-old women will be given a booster dose of the HPV vaccine, at the additional annual cost of €7 538 700 (95% CI: €7 377 200 – 7 699 247). This would increase the yearly budget to €26 026 720 (95% CI: €25 468 770 – 26 580 417) per year. In 2020, the first vaccinated cohort reaches the initial age of screening (25 years). Each subsequent year, additional screening costs will be incurred because new cohorts reach the screening age or because older cohorts are screened again, on a three-year basis. In 2060, the yearly screening costs stabilize since the first vaccinated cohort reaches 65 years and leaves the screening programme. The costs of the three-yearly screening programme for women between 25 and 65 years reaches then €25 770 360 (95% CI: €25 628 400 – 25 993 690) per year. Likewise, the treatment costs of the residual CIN 2+ and cervical cancers would increase through time, the more vaccinated cohorts accumulate. An equilibrium would be reached around the year 2080, at the annual cost of €1 681 686 (95% CI: €1 368 863 – 1 963 244) for CIN 2+ treatment and €6 708 783 (95% CI: €5 163 377 – 8 276 370) for cervical cancers treatment.

Altogether, once HPV vaccination is well established and virtually all cohorts of the population have been vaccinated, HPV vaccination with three-yearly screening is expected to cost €60 187 540 (95% CI: €58 333 540 – 62 056 220) annually.

Figure 17: Projected yearly total costs of implementing a 12-year-old girls HPV vaccination programme

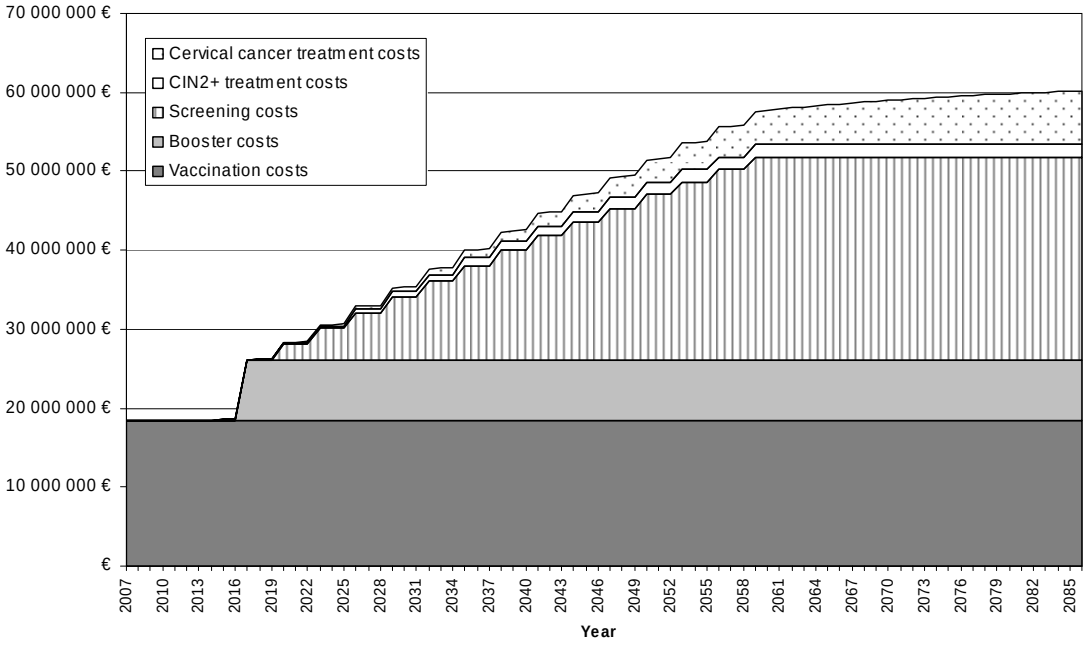
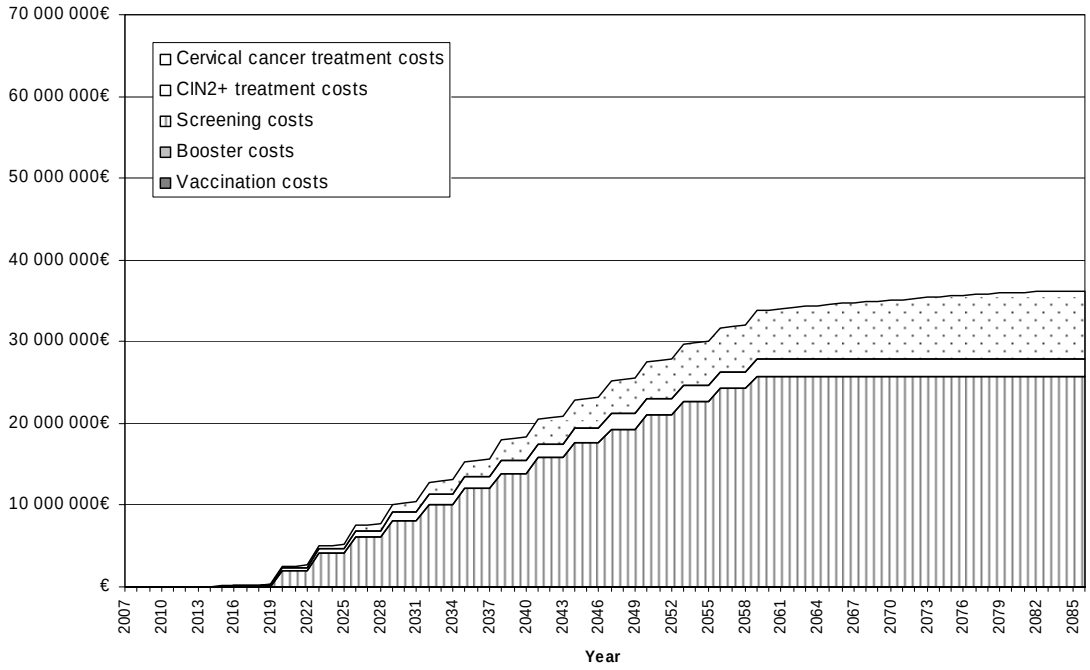


Figure 18 depicts the evolution of the budget if, from 2007 onwards, each new 12-year-old girls' cohort is not vaccinated against HPV but is screened every three years when they reach 25 years of age.

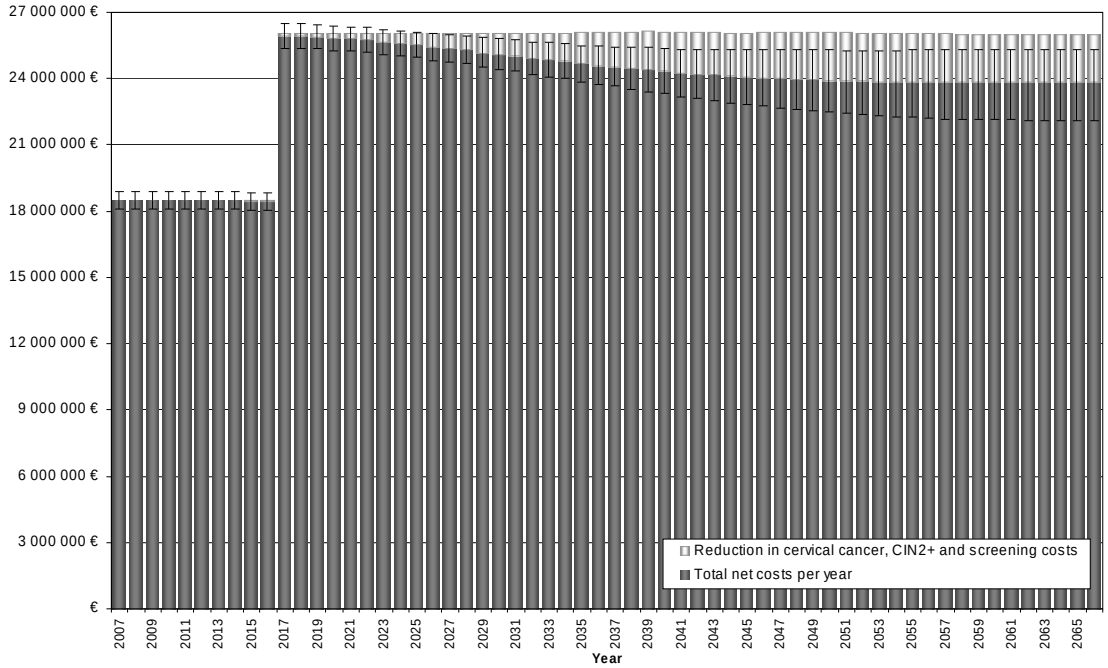
Once the three-yearly screening programme is well established and virtually all cohorts constituting the population have been through the three-yearly screening, the screening alone strategy reaches a steady-state and is expected to cost a total of €36 337 760 (95% CI: €35 108 060 – 37 613 680) per year. The breakdown of this total cost is €25 791 590 (95% CI: €25 652 580 – 26 011 080) for the screening, €2 172 596 (95% CI: €2 172 591 – 2 172 599) for the CIN 2+ treatment costs and €8 373 579 (95% CI: €7 156 765 – 9 668 135) for the cervical cancer treatment costs.

Figure 18: Projected yearly total costs of a three-yearly screening programme



The net cost to be paid by the health authorities for adding HPV vaccination over and above a three-yearly screening programme was obtained by subtracting the total yearly budget for HPV vaccination (Figure 17) by the total yearly budget of screening alone (Figure 18). The results are presented in Figure 19, where the grey columns represent the yearly total net costs and the t-bars their 95% CI. During the first 10 years, the net cost to the health authorities reaches €18 487 860 (95% CI: €18 091 570 – 18 881 170) per year, representing the investment in vaccination. The net budget then rises sharply and reaches €26 026 720 (95% CI: €25 468 770 – 26 580 417) in 2017 to account for the booster dose. Thereafter the benefits of the vaccination programme start to show their effects, mainly in terms of avoided CIN 2+ and cervical cancer treatment costs (depicted by the white columns on the graph). As a consequence, the yearly net costs slowly drop and stabilize at a total annual cost of €23 849 780 (95% CI: €22 112 780 – 25 289 300), about 50 years after the start of the vaccination programme.

Figure 19: Yearly net budget impact (and 95% CI) of starting an HPV vaccination programme



5.13 DISCUSSION

The aim of this economic model was to assess the cost-effectiveness and cost-utility of HPV vaccination in Belgium, and to evaluate the impact of uncertainty (via various scenarios and probabilistic sensitivity analyses) on the results. The results of our base-case analysis can, as such, not be compared directly with the results of models published in literature, as the discount rates for costs and effects are different. While we applied a 1.5% discount rate for effects and 3% discount rate for costs, most models use a 3% discount rate for both costs and effects as their base-case.

The chosen discount rate for effects has an important influence on the ICER. The higher the discount rate for effects, the higher the ICER, due to the fact that the benefits of vaccination occur in the future while the costs accrue in the very short term.

Our scenario with 3% discount rate for costs and effects results in ICERs that are systematically higher than the ICERs presented in literature with the same durations of follow-up and the same (or even lower) assumed efficacy duration of the vaccine. The main factors determining this difference are the assumed efficacy of the vaccine in reducing cervical cancer and CIN 2+. All studies to which we compare our results are based on more or less the same assumptions about vaccine efficacy against HPV infection. Major uncertainty exists about the potential impact of HPV vaccination on the incidence of cervical cancer. Limited data exist, however, on vaccine efficacy in reducing CIN 2+ (specific and non-specific). While we used this information on overall efficacy on CIN 2+ directly in our model, other studies modelled the impact of the vaccine on (type specific) CIN lesions through the impact on HPV. Our major concern with this approach was that very little is known about the natural evolution of HPV (see chapter 2). As such information will never become available, models have to be based on major assumptions. In our model, we tried to limit the number of assumptions by by-passing the HPV state and moving directly from 'susceptible' to 'CIN 2+' or 'cervical cancer', depending on whether women were or were not screened. Nevertheless, our model is also based on major assumptions about the natural history of cervical cancer. Hence, like other models, we cannot pretend to have found the one and only 'correct' ICER of vaccination relative to screening. But we did show that the optimistic assumptions about

vaccine efficacy, which are not and cannot be substantiated with observational data, lead to lower (better) ICERs.

Apart from vaccine efficacy, another major determinant for the ICER is the duration of protection from vaccination against HPV, CIN 2+ and cancer. In the absence of long-term data, the duration of protection and therefore the need for booster doses and whether or not HPV vaccination should be included in Belgian vaccination programmes, remains uncertain. If one assumes that primo vaccination of 12-year-old girls with 3-doses of the HPV vaccine confers lifelong immunity, our model predicts that (compared to a three-yearly screening programme) 49.3% of all cervical cancer cases (i.e. 256) and cervical cancer deaths (i.e. 85) occurring over the cohort's lifetime could be prevented. This is the most clinically efficient scenario, and also the most cost-effective one with an ICER of €14 382 (95% CI: €9 238 – 25 644) per QALY gained.

On the other hand, if one assumes that the immunity provided by the HPV vaccine wanes over time (mean duration of protection against HPV: 15 years) and booster doses are needed, the ICER of HPV vaccination versus screening alone more than doubles, because of the additional investment required for the boosters and its decreased effectiveness (20% of all cervical cancer cases, i.e. 103, and 16.4% of all cervical cancer deaths, i.e. 28, avoided with a unique booster dose). Whether one, two (or more) booster doses of the vaccine (with a 10 years interval between the doses) are required was however not found to impact much on the cost-effectiveness results. The ICER reached €32 665 (95% CI: €17 447 – 68 078) per QALY gained with one booster dose (our base-case) and €32 761 (95% CI: €19 316 – 65 734) with two booster doses.

Further this model revealed that the compliance to the screening programme after HPV vaccination was a crucial parameter. With a reduced screening coverage, potentially induced by a false sense of security, HPV vaccination could have a detrimental impact and result in more cervical cancer cases and deaths. Keeping high the screening participation rate should therefore be a priority if HPV vaccination is initiated. The introduction of a screening registry will probably increase compliance with screening, with or without HPV vaccination. Effective strategies to maintain or increase cervical cancer screening are a '*conditio sine qua non*' for the effectiveness of a vaccination programme, and monitoring the effectiveness of an HPV vaccination programme could best be achieved if there is a well organized cervical cancer screening registry.

The price of the vaccine was assumed to be lower than the price currently charged at the pharmacy in our base-case model, as we started from the premises that a vaccination programme would be organised at public level. Only in case of such a public programme, lower prices can be obtained for the vaccine. With a higher price for the vaccine, e.g. the price charged at the pharmacists (€412.2 for three doses instead of €343), the cost-per-QALY would be about €35 466 (95% CI: €21 314 - 65 928), compared to €32 665 in our base-case scenario. For the budget this means an additional cost of almost 4 million Euros per year for the initial vaccination, assuming a vaccination coverage of 84%.

According to our results and compared to screening alone, vaccination of 16-year-old girls instead of 12-year-old girls was associated with a 15.8% and 13.1% reduction in cervical cancer cases and deaths, respectively. This suggests that a temporary catch-up vaccination programme, on top of 12-year-old girls' vaccination, could still be clinically relevant. Compared to screening alone, vaccination of girls aged 16 years was, however, found to be less cost-effective than vaccination of 12-year olds, at a cost of €45 020 (95% CI: €19 601 – 138 434) per QALY gained. A higher ICER for vaccination of older age groups is consistent with findings from the literature.

Many other input parameters used in this model presented uncertainty and their simultaneous impact was assessed via probabilistic sensitivity analysis. Not surprisingly, the parameters with the greatest impact on the results were all related to vaccine effectiveness (e.g. efficacy of the vaccine in reducing CIN 2+, duration of protection against HPV after last vaccination shot, duration of evolution to cervical cancer after last vaccination shot…). This is reflected by the large confidence interval around the mean ICERs, i.e. €32 665 (95% CI: €17 447 – 68 078) per QALY gained for the base-case.

Vaccination coverage has no impact on the ICER. However, its clinical impact may not be neglected. The lower the coverage of the vaccination programme, the lower the percentage of cervical cancer cases that can be avoided. In our base-case model, a vaccination coverage of about 84% was assumed, based on Flemish data on vaccination coverage for measles-mumps-rubella (MMR). This resulted in about 20% of cervical cancers avoided by vaccination. However, the MMR vaccination at 12 years of age consists of only one dose. It is thus likely that the coverage decreases for a vaccine that requires three doses. This is indeed the case e.g. for the hepatitis B vaccination catch-up programme in the south of Belgium, with a coverage of only about 75% (personal communication B. Swennen). Lower vaccination coverage would imply a less favourable clinical outcome of the vaccination programme than the outcome presented in this report.

Based on those reported ICERs, how can we make a judgement whether or not HPV vaccination in Belgium is cost-effective? There are indeed theoretical and pragmatic difficulties in eliciting a fixed ICER threshold below which a technology would automatically be defined as cost-effective.[116] Acceptability of a technology is not determined by the ICER only but depends on other factors as well, such as, for instance, the target population, number of people affected, lethality of the disease etc. Hence the decision making process is much more complicated than the adoption of a single ICER threshold above which an intervention is worth reimbursing and underneath which it is not. Therefore, in Belgium, no such threshold has been defined so far. In the UK however, since 1999, NICE has adopted a cost-effectiveness threshold range of £20 000 to £30 000 per QALY gained[117]:

- ICER < £20 000 (€30 000): intervention likely to be accepted
- ICER between £20 000 - £30 000 (€30 000 - €45 000): needs additional factors (e.g. the innovative nature of the technology, the particular features of the condition and population receiving the technology) to justify acceptance of the intervention
- ICER > £30 000 (€45 000): the case on the additional factors has to be extremely strong to justify acceptance of the intervention.

If we appraise the results of our scenario with a 3% discount rate for costs and effects, i.e. the base-case scenario in the UK, against the NICE thresholds, it is unlikely that an HPV vaccination programme in Belgium would be considered as readily acceptable, as there is more than 96% probability that the ICER is above €30 000 per QALY. There is almost 65% probability that the ICER is above €45 000 per QALY gained. In case of lifelong protection against HPV from vaccination, the point estimate of the ICER is €26 786 per QALY, with the 95% C.I. ranging between €17 386 and €47 912 per QALY. In this context, and considering the increasing concerns that the NICE threshold values might be too high[118], it is unlikely that HPV vaccination would be granted much priority based on cost-effectiveness considerations. Reimbursement of the vaccine would require other arguments than pure economic ones.

Compared to other economic evaluations of vaccine-preventable diseases performed in a Belgian setting, HPV vaccination appears less cost-effective than pneumococcal vaccination but more cost-effective than rotavirus vaccination. Fully funded universal rotavirus vaccination was indeed estimated to cost between €50 024 (95% CI: €25 374 – 99 730) and €68 321 (95% CI: €35 982 – 132 635) per QALY gained, depending on the vaccine used (health care payer perspective),[119] while universal pneumococcal vaccination of the 2+1 schedule was estimated to cost about €10 000 per QALY gained.[120]

From the budget-impact analysis, it was estimated that if HPV vaccination (initial vaccination plus a booster 10 years later) of 12-year-old girls starts in 2007, the net cost to the health authorities, over and above the three-yearly screening programme, would stabilize around €23.8 (95% CI: €22.1 – 25.2) millions per year. These are additional costs that need to be borne by the health care budget if the vaccine and booster is entirely reimbursed, implying €23.8 million less available for other health care interventions. Even if the health care budget increases from year to year, this

expenditure represents an opportunity cost for other possible uses of these resources. Current RIZIV/INAMI budget expenditures related to opportunistic cervical cancer screening appear much higher than the expenditures of the three-yearly programme as used in our model. Therefore, in theory, an HPV vaccination programme could at least partly be financed based on the same RIZIV/INAMI budget, provided that the appropriateness of screening practices is improved.

Inevitably this model has its limitations. Our model is a static cohort model, which prevents us from addressing population-related issues, such as universal (i.e. girls and boys) HPV vaccination or catch-up vaccination since herd immunity effects are ignored. This choice for a static model was however mainly motivated by of the lack of current data to populate a dynamic model (such as the sexual contact matrix) and by the uncertainties around the natural history and evolution of HPV infections.

The possibility for HPV strains interaction (cross-protection or strain replacement) was not explicitly modelled, nor the impact of the vaccine on genital warts and other HPV-related cancers. As in other HPV vaccination models, many uncertainties remain in the input parameters, the most important one being the natural history of cervical cancer. The natural evolution of cervical cancer will, however, never be documented with observational data because of ethical reasons. We therefore had to base the input values for the natural history of cervical cancer on the best available '*educated guesses*'.

The reduction of possible treatments for CIN 1 and of pregnancy complications after CIN treatment, the reduction in conisations in case of CIN 2+ lesions in younger women, the prevention of genital warts, and potentially also other HPV-related cancer types were not included in the model. As a consequence, costs might be slightly overestimated and outcomes underestimated. The impact on the ICER would be that they become slightly better.

The strength of this model is that it avoids, as much as possible, to rely on potential transition probabilities for which little evidence is available. As such, this model bypasses the intermediate state HPV infections, whose incidence and evolution to cervical cancer are still highly uncertain, and directly simulates the impact of vaccination on 'final' endpoints (CIN 2+ and cervical cancers) for which Belgian data are available. Since we bypass the HPV infection, our model becomes, implicitly, a SIS model. Another advantage of the current model, which is linked to the previous, is that it assesses the impact of HPV vaccination on the global incidence of CIN 2+ lesions and cervical cancers, and not just on those specific to the vaccine types (HPV16/18-specific outcomes).

5.14 CONCLUSIONS

In conclusion, under the hypothesis of decreasing immunity and assuming that screening compliance remains unchanged in the post HPV vaccination era, the implementation of an HPV vaccination programme in Belgium is estimated to have a cost-effectiveness ratio of €32 665 (95% CI: €17 447 – 68 078) per QALY gained. The yearly net investment would be around €23.8 million (95% CI: M€22.1 – 25.2) per year, after reaching a steady state situation. This would be in case of a public vaccination programme comparable to, for example, the MMR vaccination programme.

Major uncertainties exist about the cost-effectiveness of the vaccination programme. This is, amongst others, related to uncertainty about the natural history of cervical cancer, the duration of protection of vaccination and the vaccine efficacy. These uncertainties create large confidence intervals around the ICERs and hamper clear-cut conclusions about the economic desirability of a large-scale vaccination programme.

Key points

- **Our economic model was intended, contrary to most published models to evaluate the effect on all cervical cancers not only those related to vaccine type specific cancers. Moreover, our aim was to explore uncertainty related to unsure assumptions. We adopted an original approach, eliminating the infection – precancerous lesion – cervical cancer pathway. We directly modelled both the precancerous lesion and cervical cancer outcomes from the susceptible state based on the published decrease in overall CIN 2+ lesions.**
- **The model relates to a publicly organised vaccination programme only. Its results are not relevant for a strategy of opportunistic vaccination. Further this model was populated with efficacy data from Gardasil trials only. If Cervarix efficacy data on cervical cancer would be comparable to Gardasil data, the model would also apply to this product since no assumptions were made on Extra Genital Lesions (EGL).**
- **Assuming decreasing protection of the vaccine over time, and with discount rates of 3% for costs and 1.5% for outcomes, HPV vaccination in Belgium is estimated to cost between €32 665 (95% CI: €17 447 – 68 078) per QALY gained with one booster dose, and €32 761 (95% CI: €19 316 – 65 734) per QALY gained with two booster doses.**
- **Assuming vaccine lifelong immunity, HPV vaccination in Belgium is estimated to costs €14 382 (95% CI: €9 238 – 25 644) per QALY gained.**
- **Keeping screening compliance rates at high levels should be a major priority even when HPV vaccination is implemented. Introducing a cervical cancer screening registry could help maintain or even improve screening coverage. Monitoring the effectiveness of a HPV vaccination programme could best be achieved if there is a well organized cervical cancer screening and vaccination registry.**
- **After a period of stabilization, HPV vaccination (initial vaccination at 12 years plus a booster at 22 years or age) would represent a yearly net investment of €23.8 million (95% CI: M€22.1 – 25.2) to the health authorities.**
- **Current RIZIV/INAMI budget expenditures related to opportunistic cervical cancer screening are higher than an optimal screening scenario entirely based on the current guidelines. In theory, a HPV vaccination programme could largely be financed based on the same RIZIV/INAMI budget if costs for screening were better controlled.**
- **Compared to published models, our model predicts higher cost-effectiveness ratios if –as in most models in literature- both costs and effects are discounted at 3%.**
- **There are major sources of uncertainty that cannot be solved, with current evidence. These cumulated uncertainties create large confidence intervals around the point estimates for the ICERs and therefore hamper clear-cut conclusions.**

6 ETHICAL AND ORGANISATIONAL ISSUES

6.1 ETHICAL AND PATIENT ISSUES

We used the ethical framework proposed by Beauchamp and Childress.[121]

- non-malevolence (do not harm)
- beneficence (do good)
- respect for autonomy and patient issues
- justice

Other base references for this chapter are Zimmerman et al.,[122] de Molo-Martin et al,[123] and Colgrove et al.[124]

6.1.1 Non malevolence and beneficence

Non malevolence (*'primum non nocere'*[e] - rule in medicine *'First do not to harm'*) requires that health care workers and others refrain from intentionally causing harm (for instance killing a prisoner to use his organs to save another life is not morally justifiable). Beneficence, in the field of health policy – such as making an HPV vaccine available and financially accessible to a given population – refers to balancing benefits, costs, and risks. Cost-effectiveness and cost-benefit analysis, although controversial,[f] are widely used tools to try to answer this question.

There is an important degree of uncertainty about the exact balance between benefits, costs, and risks of HPV vaccination (see chapters on cost-effectiveness). Reasonable evidence exists for the benefits of HPV vaccine on preventing cervical dysplasia, especially dysplasia associated with vaccine type HPV genotypes, but the evidence is surrounded by a wide confidence interval. Moreover, the *'ex-officina'* cost of the vaccine is important (€412 for a 3-dose immunisation).

What are the risks? Trials did not detect any safety signal of concern, but still this should be interpreted with caution. Large numbers of vaccine doses will be administered, and even a very low risk could translate into an unacceptable number of vaccine-related problems, in particular given that this is a preventive intervention targeting healthy young girls. Assuming for instance that the risk of a serious adverse events (SAE) would be 1/10 000, undetectable with current trials, this would mean that with the immunisation of a cohort of 50 000 healthy young girls every year in Belgium, we could expect 5 cases of vaccine-related serious adverse events per year. Although unlikely with current evidence, this is a risk that cannot be ignored, and a risk that, especially in public perception, could seriously jeopardize other maybe more essential vaccinations.

Other possible risks relate to possible behavioural changes induced by vaccination, but these are obviously speculative as they have not been studied. For instance, the possibility that the HPV vaccine could create a false sense of security against sexually transmitted infections (STI) and increase teenager sexual activity has sparked a big debate particularly in the US where some groups oppose the vaccine mainly on moral grounds.[125] However, from all considerations women take into account when deciding to have sex, a vaccination many years previously in the case of teenage girls, seems unlikely to rank high. We are aware that this reasoning is only common sense and not directly supported by evidence since the vaccine was introduced too recently. However, there are enough other reasons to promote safe sex also without considering HPV infection and potential cervical cancer years later.

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e Attributed by some to Hippokrates of Kos (about 460 to 370 BC) a.k.a. Ἱπποκράτης.

f Critics claim that these methods of analysis are not sufficiently comprehensive, that they fail to include all relevant values and options, that they are often themselves subjective and biased, and that they concentrate decision making authority in the hands of narrow, technical professionals who often fail to understand moral, social, legal, and political constraints that legitimately limit use of these methods.[121]

Another theoretical risk is that a false sense of security would lead to reduced compliance with cervical cancer screening programmes. Again in the case of young girls the long delay between vaccination and the start of the screening makes this rather unlikely. However, monitoring both vaccination status and screening attendance through a population register containing both is indicated given the current uncertainty of long term vaccine effectiveness and safety.

6.1.2 Respect for autonomy

6.1.2.1 Respect for autonomy and informed decision making

Much of the discussion on respecting autonomy revolves around informed decision making. For a new technology such as HPV vaccination with so much uncertainty involved, and potentially contentious moral issues all information relevant to support decision making needs to be provided.

The exact content of the information needs to be identified by health professionals, but it should obviously provide a fair assessment of benefits, risks, and uncertainties. For HPV vaccination it should at the minimum include that:

- the vaccine has demonstrated protection against approximately half of precancerous lesions (not against cancer itself)
- with current evidence the duration of protection is unknown, and that therefore a booster might be needed
- regular cervical cancer screening remains necessary.

In a survey of parental attitudes towards HPV vaccination of their children in the UK, information given to the parents was mainly about HPV infection and its consequences, the only information about the vaccine itself was that 'vaccination will prevent cervical cancer'.[126] In another, similar study the fact sheet given to the parents included statements such as 'trials of vaccination have shown it to be 100% effective against HPV'.[127] In these two examples the information provided cannot be considered valid and sufficient to form the basis of an informed choice.

6.1.2.2 Patient issues: attitudes towards HPV vaccine, and factors associated with acceptance.

For this section we refer mainly to the corresponding part of the Danish HTA report on HPV vaccination.[92] This report studied the attitudes of parents regarding vaccinating their children, and the attitude of young people regarding their own vaccination. It was based on a systematic literature review, and on a qualitative study among Danish parents and youngsters.

The systematic literature review covered various databases for literature published between January 2000 and March 2007 and identified 16 primary studies relevant to the subject. Of these 16 studies, 11 were conducted in the USA, 4 in the UK, and 1 in Australia. Results are presented as a narrative summary (Table 51).

Table 51: Narrative summary of the systematic literature review on attitudes towards HPV vaccination. Adapted from the Danish HTA.[92]

…there is overall a high degree of acceptance of HPV vaccination among the parents, and most would have their children vaccinated. The acceptance of the vaccine depends on knowledge about HPV infection and the connection with cervical cancer and especially on knowledge about, and confidence in, the safety and effect of the vaccine. Some American studies find that worries that HPV vaccination may encourage promiscuity in their children might be an obstacle to parents' acceptance. Another aspect influencing the attitudes to HPV vaccination is parents and young people's assessment of risk: whether they think that it is probable and serious to contract HPV infection and cervical cancer. Some studies also find that the price of the vaccine influences whether parents want the vaccine for themselves or their children. Other aspects that influence whether parents will have their children vaccinated are the children's age and gender and whether the parents have any personal experience with sexually transmitted infections or cancer.

An RCT not included in the Danish report, about providing written information about HPV to parents did in fact improve knowledge, but did not improve acceptance of the vaccine.[128]

A summary of focus group discussions in Denmark on acceptance of vaccination is given in Table 52.

Table 52: Circumstances found significant for the acceptance of HPV vaccination. Focus group discussions of Danish parents and youngsters Adapted from the Danish HTA report.[92]

• Confidence in the safety of the vaccine
• Linking with the existing childhood immunisation programme
• Vaccination is offered to both genders
• Price
• Equal access to the vaccine
• Optimal age: 12 years. Reasons are (apart from the fact that this population is supposed to be largely sexually naïve) that children this age are mature enough for the parents to discuss this vaccination with them, but also for operational reasons (link with MMR immunization)
• Knowledge about the HPV vaccine and HPV-related diseases, assessment of risk of HPV infection and of cervical cancer, assessment of the seriousness of HPV infection and of cervical cancer
• Personal experience of cancer in the immediate family/circle of friends
• Normalisation of HPV vaccination, i.e. focus on cancer rather than on the sexual transmission

6.1.2.3 Discussion and conclusion

Most of the literature on the subject of attitudes towards HPV vaccination is based on the underlying assumption that the vaccine *should be used*, and aims at building knowledge on how to improve acceptance. But the balance between the benefits and risks of the vaccine is not overwhelmingly clear, and providing proper information to support (parental) choice is in this case an end in itself, and not a way to improve acceptance. Clearly the content of the information to be provided is critical – examples from the published literature show how this information can be inadequate or even downright false. Defining the contents of this information for Belgium deserves careful consideration.

6.1.3 Justice

Justice in health care is a complex concept, and it is beyond the scope of this chapter to develop these issues fully. We will only address a few points.

One aspect deals with the allocation of resources and priority setting (distributive justice). Within a utilitarian framework – providing the greatest health benefit for the money expended – the classical tool used for priority setting is cost-effectiveness analysis (CEA). We refer to the relevant chapter of this report for a full discussion on the results of the cost-effectiveness analysis of HPV vaccines, but clearly there is much uncertainty as to whether HPV vaccines do indeed provide 'the greatest benefit for the money spend'.

Another aspect of justice has to do with social inequalities in health and access to care. Social inequalities in the risk for cervical cancer, and access to screening are well described (see chapter on epidemiology) and although these have not been studied in Belgium, there is no reason to believe that the situation is different in our country. If universal coverage of the vaccine can be achieved, it could help to partially redress of the consequences of these social inequalities.

6.2 ORGANISATIONAL ISSUES

6.2.1 Dosage and administration of HPV vaccines

Gardasil should be administered intramuscularly as 3 separate 0.5 ml doses according to the following schedule: first dose at elected date, second dose 2 months later, third dose 6 months after the first dose. It is not currently known whether and at what moment a booster will be needed.

6.2.2 Recommending vaccination vs. reimbursing the vaccine

Recommending vaccination as an effective intervention by the Belgian Superior Health Council,[129] was done on the basis of efficacy and safety data. Funding by society however takes into account the cost-effectiveness and budget impact of the intervention. Therefore, recommending vaccination does not necessarily imply that society should also pay for it.

On the basis of existing efficacy data, the vaccine could be recommended to unexposed females. Its high cost however will act as a strong deterrent unless society bears all or part of this cost. On the other hand the budget impact could be high and the cost-effectiveness of the vaccine is uncertain.

The discussion below intends to provide some basis for decision-making when it comes to setting criteria for refunding HPV vaccines, should the decision to refund it be taken.

6.2.3 Target population and implementation: for which age group should society pay for the vaccine?

In the absence of data, it is too early to consider vaccination of males. Males could in theory be vaccinated to prevent genital warts, but mainly to prevent transmission of the virus.

Females who have not yet been exposed to HPV types included in the vaccine are those most likely to benefit from the vaccine, irrespective of their age, to the extent that they are or will be sexually active and therefore at risk of being exposed to HPV infection after being immunised. It follows that for decision-makers, setting an upper (and lower) age limit beyond which society would or would not pay for the vaccine will be made for practical reasons and will by necessity involve some degree of arbitrariness and uncertainty because age alone is an imperfect proxy for sexual behaviour and potential exposure to HPV infection.

The rationale to define a specific age-group for which the society should pay for the vaccine is different according to the context in which the vaccine is to be given. Defining age groups for a universal vaccination programme to be implemented through school medicine is made on the basis of *a population risk assessment*. The rationale for

age limits could in theory be different if *an individual risk assessment* is made (for instance by a GP). Risk assessment refers here to the risk of previous exposure to HPV.

Additionally in Belgium the decision to add a vaccine to the immunisation programme recommended for children (and paid for by society) is separated from the decision to reimburse certain medical products (such as vaccines) as it involves different bodies and different decision levels (federal level and community level).

We will briefly discuss possible criteria to refund the vaccine according to the context it is to be given.

6.2.3.1 Which age groups should be the target for a universal HPV vaccination programme to be implemented through school medicine in Belgium?

The rationale for a universal vaccination through school programme is:

- universal vaccination programme is the best strategy for insuring maximum coverage, in particular among underprivileged populations.
- vaccine is cheaper (bulk purchase)

The choice of the school year should be based on the proportion of the cohort having started sexual debut, and ease of implementation. In a survey conducted in Belgian schools in 2002, 4-6% of 12-14 year old girls reported having already experienced sexual intercourse.[130, 131] If it is decided to implement a universal immunisation programme in young girls through school medicine, then it makes sense to target girls no older than 12 years.

The infrastructure and experience in universal vaccination of young girls do already exist in Belgium (this is being done to catch-up on hepatitis B immunization). In this model, vaccination is proposed through school medicine; parents are given the option to have their children immunized through school medicine or alternatively by a private practitioner (see recommendations of the Belgian Superior Health Council).[129] Catch-up Hepatitis B immunisation is organised in 6th year primary in French-speaking Belgium (average age of pupils is 12 years), and first year secondary (average age is 13 years) in Flanders. It is feasible to organize a full course (3 doses) over one school year.

The question that arises is whether a one-time catch-up programme for (slightly) older girls should also be organised in schools. If 12-year old are to be immunised in routine, is there a rationale for, or against organising a one-time catch-up programme for 13 to 15 year-olds?

The efficacy of the vaccine in girls 13 year and older is lower because some will already be infected with HPV 16/18, while the immune protection may cover a greater part of the sexually active life when started later. Both aspects have been included in the model and they counteract. We modelled this ICER for 16 year old girls and it was less favourable compared to vaccination of 12 year olds (see chapter: economic evaluation).

Some other considerations could influence the decision to organize a one-time catch-up programme for girls older than twelve:

- It remains uncertain whether immunising 12 year-old is cost-effective. Decisions are often made in the context of uncertainty, and the question is how much uncertainty decision makers are ready to bear.
- Budget impact.
- Operational difficulties. For instance the need for a booster is not known. Should a booster turn out to be needed, 10 years after the first cohort has been vaccinated, it will be more difficult to organise recall programmes for several cohorts at the same time.

6.2.3.2 *For which age-group should the vaccine be reimbursed by society outside a school programme?*

An upper age limit over which the vaccine would not be refunded by the social security cannot be defined on a scientific basis because the real criteria for judging whether the vaccine will be useful for a given person is not her age, but her risk of having been previously exposed to HPV infection. Moreover, the vaccine has not been tested in women older than 26 years. A 20-year old virgin would in theory benefit from the vaccine whereas a 18 year-old with an history of several sexual partners would be less likely to benefit.

Testing for previous exposure to HPV vaccine strains is not routine practice but there is no theoretical reason why it could not be done. Testing is expensive but so is the vaccine. A simple 'back of the envelope' calculation shows that, assuming that 25 % of females have already been exposed (such as in the trials), testing 4 females (estimated cost: €60 per test *4 = €240), with one being found positive and therefore not eligible for the vaccine would still be cost saving. Although such testing could detect only current exposure to infection (and not past exposure), it could be argued that it was the criterion used in the trials[g].

The advantage of delivering the vaccine through the network of private practitioners is that an individual risk assessment could in theory be made. The disadvantages are that the vaccine costs will be higher, and coverage will be less (and possibly biased along a socio-economic gradient). This report did not specifically analyse the cost-effectiveness of a vaccine delivered outside a school programme, but because of its higher costs it can only be less favourable than a vaccine delivered through school programmes.

The decision to prescribe the vaccine will be also influenced by the attitudes and knowledge of both prescribers and their patients. Intensive marketing campaigns and media coverage are conveying an overoptimistic picture of the benefits of the vaccine[132, 133] which could influence and are expressely intended to influence prescribing behaviour. In Belgium, media announced 'the end of cervical cancer',[134] or that 'Gardasil shows up to 100% efficacy in the prevention of cervical cancer'.[135]

HPV vaccination is expensive, and all females are potentially at risk of cervical cancer. If no criteria are set for refunding, inadequate prescribing could have a serious impact on public financial resources. The challenge for decision makers is to decide on criteria for reimbursement or for vaccination campaigns that limit the risk of inadequate use of the vaccine while making the vaccine accessible to those that are most likely to benefit. Defining an age limit will be arbitrary but will make it easier to implement and control.

6.2.4 Monitoring and surveillance

Ideally a link should be established between a vaccination register and a cervical cancer screening register to assist in the long-term evaluation of the vaccination strategy. These registers do not yet exist although in Flanders there is a register for child vaccination, and linkage raises some confidentiality issues that need to be resolved. In addition, epidemiology of HPV should also be the target for a surveillance system.

6.2.5 Conclusions

Immunisation through a school programme can insure a better coverage, particularly for underprivileged groups, and is also more cost-effective because of scale economy when purchasing the vaccine.

Cost-effectiveness analyses lack the power to discriminate between the cost-effectiveness of immunising different age cohorts. The decision to organize one catch-up programme should be based on other considerations such as the uncertainty involved, the budget impact, and operational issues.

Delivering the vaccine through private practitioners will have a less favourable cost-effectiveness ratio because of higher vaccine costs. Intensive marketing campaign and

g A small proportion of participants was seropositive but not DNA positive

media coverage are conveying an overoptimistic picture of the benefits of the vaccine which are intended to influence prescribing behaviour but could also influence participation rates in cervical cancer screening. The challenge for decision makers is to identify criteria for reimbursement insuring access to those who could benefit from the vaccine while preventing overuse of the vaccine.

Key points

- **The balance between benefits, risks, and costs for the HPV vaccine is not overwhelmingly clear. The ethical principle of *'do not harm'* is particularly important when considering a mass intervention on *healthy* young girls.**
- **Given the uncertainties associated with HPV vaccination, the overly optimistic picture conveyed by the media, and potentially contentious moral issues, it is crucial that independent and correct and complete information will be provided, to enable true *informed choice*. Providing adequate information should be seen as an end in itself, not as a way to improve acceptance. The content of the information deserves careful consideration.**
- **Universal immunisation implemented through an official vaccination programme can allow for a better coverage, particularly of underprivileged groups. This is particularly important given that underprivileged groups are at higher risk of cervical cancer, and less likely to be screened (ethical principle of justice).**
- **Universal immunisation implemented through an official vaccination programme can secure a lower cost of the vaccine through bulk purchase. Delivering the vaccine outside an organised programme (opportunistic vaccination) will be less cost-effective because of the higher cost of the vaccine.**
- **Economic analyses using static cohort models, as done in this report, are limited in their potential to define specific age thresholds for one-time catch-up programmes for older cohorts. For those decisions the associated uncertainty on efficacy and cost-effectiveness, the budget impact, and the operational feasibility should be considered.**
- **Defining age criteria to reimburse the vaccine outside an organised programme can only be made for pragmatic reasons because age is not a criterion to identify, among sexually active females, those likely to benefit from the vaccine.**
- **Introducing a combined vaccination and screening registry could help maintain or even improve screening coverage and could enable monitoring the effectiveness and safety of a HPV vaccination programme.**

7 APPENDICES

APPENDICES FOR CHAPTER ON EPIDEMIOLOGY (CHAPTER 2)

APPENDIX 1: EPIDEMIOLOGICAL CLASSIFICATION OF HPV TYPES

The evidence for the carcinogenic role of HPV infections comes primarily from case-control studies. The risks for cervical cancer associated with HPV type-specific infection have been estimated using pooled data from 11 case-control studies with similar protocols from nine countries. The epidemiological classification of HPV types into 'high-risk' and 'low-risk' types based on these data correlated fairly well with the phylogenetic classification (to the exception of HPV 70 and 71)[136, 137].

Epidemiological classification of HPV types

Group	HPV types
Established high-risk, or oncogenic type. (High odds ratio – OR- based on at least 10 cases of cervical cancer positive for the type being analyzed)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably high-risk (OR based on less than 10 cases)	26, 53, 66, 68, 73, 82
Established low-risk Moderately increased OR, not statistically significant; or types detected only in controls.	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

Source: Munoz[137]

APPENDIX 2: DISTRIBUTION OF SINGLE AND MULTIPLE HPV INFECTIONS BY HPV TYPES

Distribution of single and multiple HPV infections by histology of cervical cancer[h]

	N	%	Cumulative %
Squamous Cell Carcinoma (SCC)			
Total single infections	2461	92%	
HPV 16	1452	54%	54%
HPV 18	301	11%	66%
HPV 45	139	5%	71%
HPV 31	102	4%	75%
HPV 52	60	2%	77%
HPV 33	55	2%	79%
Other	352	13%	92%
Total multiple infections	209	8%	
Multiple: HPV 16-18	47	2%	
Other	162	6%	
Total SCC	**2670**	**100%**	
Adenocarcinoma and adenosquamous carcinoma (ADC)			
Total single infections	*172*	*93%*	
HPV 16	77	42%	42%
HPV 18	69	37%	79%
HPV 45	11	6%	85%
HPV 59	4	2%	87%
HPV 31	2	1%	88%
Other	9	5%	93%
Total Multiple infections	*13*	*7%*	
HPV 16+18	5	3%	
Other	8	4%	
Total ADC	**185**	**100%**	
All cancers (SCC+ADC)			
HPV 16	1529	54%	54%
HPV 18	370	13%	67%
HPV 16+18	52	2%	68%
Other	904	32%	100%
Total SCC+ADC	**2855**	**100%**	

Source: adapted from Munoz[22]. Note that the quote 'HPV 16 and 18 are responsible for 71% of cancers worldwide' does not refer to these prevalence data but to theoretical estimations based on region-specific HPV distribution in cervical cancer, and incidence of cancer.

h Slightly different data are also available from meta analyses [31] [138]. These meta-analyses pool together data collected with different HPV testing procedure, the reason why we preferred to present data from Munoz.[22]

APPENDIX 3: NUMBER OF HPV-RELATED CANCERS IN BELGIUM, BY AGE, TYPE AND REGION

Invasive tumours in females per localisation, age group, and region in Belgium, for the year 2003. Number of cases

		Tot	00-14	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+
Flemish region																		
C10	Oropharynx	4	-	-	-	-	-	1	-	-	1	-	1	-	-	1	-	-
C21	Anus and anal canal	48	-	-	-	1	2	1	2	3	6	9	2	3	4	9	3	3
C51	Vulva	87	-	-	-	2	-	4	7	1	3	5	6	9	9	13	13	15
C52	Vagina	22	-	-	-	-	-	-	1	1	1	1	3	2	5	5	1	2
C53	Cervix uteri	356	-	-	3	9	29	42	45	42	41	27	16	24	27	22	15	14
Walloon region																		
C10	Oropharynx	15	-	-	-	-	-	-	3	2	3	1	2	3	1	-	-	-
C21	Anus and anal canal	23	-	-	-	-	-	1	1	-	3	4	3	1	3	1	3	3
C51	Vulva	36	-	-	-	-	1	-	1	3	2	-	2	3	9	10	4	1
C52	Vagina	11	-	-	-	-	-	-	-	1	3	-	-	1	3	1	1	1
C53	Cervix uteri	180	-	1	-	8	14	23	20	19	13	13	11	17	13	15	7	6
Brussels Capital Region																		
C10	Oropharynx	2	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-
C21	Anus and anal canal	7	-	-	-	-	-	-	-	-	-	-	1	1	1	3	-	1
C51	Vulva	8	-	-	-	1	-	-	-	-	1	1	-	-	-	2	-	3
C52	Vagina	3	-	-	-	-	-	-	1	-	-	-	-	-	-	1	1	-
C53	Cervix uteri	59	-	-	-	1	4	4	8	7	3	10	3	3	7	5	1	3

Source: Belgian Cancer registry. http://www.registreducancer.org/

Selected invasive tumours in females per localisation, age group and region. Belgium, 2003. Incidence rates.

		Tot	00-14	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+	CR	ESR
Flemish region																				
C10	Oropharynx	4	-	-	-	-	-	0	-	-	1	-	1	-	-	1	-	-	0	0
C21	Anus and anal canal	48	-	-	-	1	1	0	1	1	3	5	1	2	3	7	3	4	2	1
C51	Vulva	87	-	-	-	1	-	2	3	0	2	3	4	6	6	10	14	22	3	2
C52	Vagina	22	-	-	-	-	-	-	0	0	1	1	2	1	3	4	1	3	1	0
C53	Cervix uteri	356	-	-	2	5	14	18	19	19	21	15	11	15	17	17	17	20	12	10
Walloon Region																				
C10	Oropharynx	15	-	-	-	-	-	-	2	2	3	1	3	4	1	-	-	-	1	1
C21	Anus and anal canal	23	-	-	-	-	-	1	1	-	3	4	4	1	3	1	5	8	1	1
C51	Vulva	36	-	-	-	-	1	-	1	2	2	-	3	4	10	13	7	3	2	1
C52	Vagina	11	-	-	-	-	-	-	-	1	3	-	-	1	3	1	2	3	1	0
C53	Cervix uteri	180	-	1	-	8	12	19	16	15	11	13	14	21	15	19	12	15	10	9
Brussels region																				
C10	Oropharynx	2	-	-	-	-	-	-	-	-	-	-	5	5	-	-	-	-	0	0
C21	Anus and anal canal	7	-	-	-	-	-	-	-	-	-	-	5	5	4	14	-	7	1	1
C51	Vulva	8	-	-	-	2	-	-	-	-	3	4	-	-	-	9	-	20	2	1
C52	Vagina	3	-	-	-	-	-	-	3	-	-	-	-	-	-	5	6	-	1	0
C53	Cervix uteri	59	-	-	-	2	9	11	23	22	10	37	14	14	31	23	6	20	11	11

CR: crude (all ages) incidence rate (n/100 000 person years)
ESR age standardized incidence rate, using the European Standard Population (n/100 000 person years)
Source: Belgian Cancer registry. http://www.registreducancer.org/

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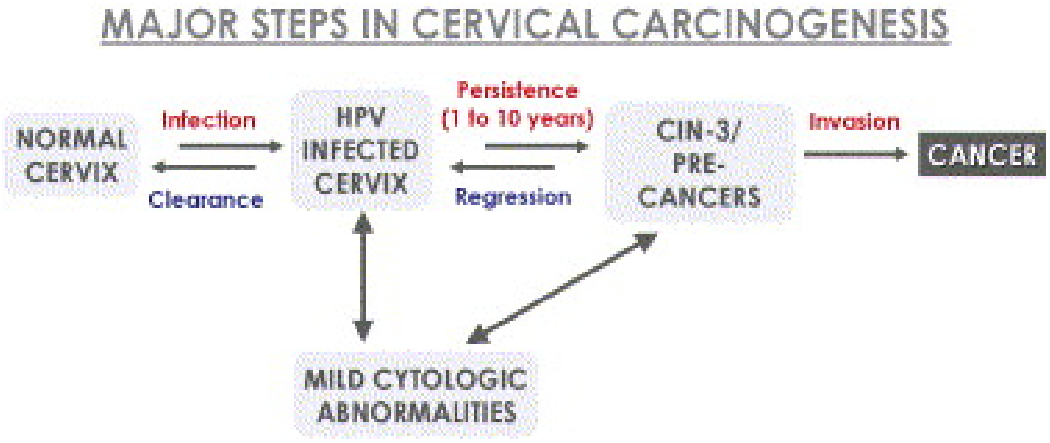
APPENDIX 4: STEPS IN CERVICAL CARCINOGENESIS

Pre-malignant changes represent a spectrum of histological abnormalities ranging from CIN 1 (cervical intraepithelial neoplasia grade 1, or mild dysplasia) to CIN 2 (moderate dysplasia) to CIN 3 (severe dysplasia, carcinoma in-situ). However this is not, as was once believed, one of progression of CIN 1 to CIN 2 to CIN 3 and eventually to invasive cancer.

Steps in cervical carcinogenesis



Infection of the metaplastic epithelium of the cervical transformation zone with one of the carcinogenic types of HPV infection; this infection is either cleared quickly through either the innate immune system or other mechansisms. The majority of established infections which often manifest as microscopoic abnormalities are then either cleared at some point by host immune responses. Viral persistence leads to clonal progression of the persistently-infected epithelium and cervical intraepithelial neoplasia (CIN)-3/precancers arise; events which remain unknown lead infected cells to cervical invasion. Source: Moscicki[21]

APPENDICES FOR CHAPTER ON EFFICACY AND SAFETY (CHAPTER 3)

APPENDIX 1: PUBLISHED LITERATURE - SEARCH STRATEGY.

The search was conducted on March 30, 2007 and covered publications since the year 2000 included in Medline, Embase, and the Cochrane Controlled Trials Register. The search strategy for each database is described below.

Literature search for HPV vaccine: search strategy

		Hits
Medline		
1	Viral Vaccines/	6 017
2	exp Papillomaviridae/	8 491
3	1 and 2	559
4	Papillomavirus Vaccines/	353
5	3 or 4	703
6	limit 5 to humans	606
7	limit 6 to (case reports or comment or editorial or guideline or in vitro or interview or letter or news or newspaper article or 'review')	339
8	6 not 7	267
9	limit 8 to yr='2000 - 2007'	243
Embase		
1	'virus vaccine'/de AND [humans]/lim AND [abstracts]/lim AND [embase]/lim AND [2000-2007]/py	1 389
2	'papilloma virus'/exp AND [humans]/lim AND [abstracts]/lim AND [embase]/lim AND [2000-2007]/py	5 732
3	#1 AND #2 AND ([editorial]/lim OR [letter]/lim OR[review]/lim) AND [embase]/lim	127
4	#2 NOT #3	159
CRRCT		
1	MeSH descriptor **Viral Vaccines** explode all trees	2 661
2	MeSH descriptor **Papillomavirus** explode all trees	229
3	(#1 AND #2) – clinical trials	24

APPENDIX 2: CONTRIBUTION OF RETRIEVED ARTICLES TO STUDY OBJECTIVES

Most articles retrieved by the search strategy described above were rejected based on title or abstract (main reason for exclusion: not a RCT, or phase 1 RCT). The remaining studies are detailed below.

HPV vaccine literature search: studies selected and their contribution to study objectives

	Contribution to study objective			Comment
	Efficacy	**'Bridging'**	**Safety**	
HPV 16 component of Gardasil (protocol 005)				
Mao 2006[62]	Yes	No	No	Update of Koutsky, but refers to Koutsky for safety data.
Koutsky 2002[61]	Yes	No	Yes	Limited data on clinical adverse events during 2 weeks after any vaccination
Poland 2005[139]	No	No	No	Efficacy: immunologic endpoints only Limited data on clinical adverse events during 2 weeks after any of vaccination, but sample size smaller than Koutsky
Fife 2004[140]	No	No	No	Study of 2 monovalent vaccines (11/16) HPV 16= same as Prot 005. Sample size smaller than Koutsky
Gardasil				
Villa 2006[37]	Yes	No	No	Protocol 007. Update of Villa 2005. Efficacy: data on EGL only, no CIN 2+. No data on safety/tolerability, refers to other studies (Villa 2005,2006).
Villa 2006 [66]	No	No	Yes	Protocol 007. Efficacy: Immunological endpoints only. Safety/tolerability: detailed data
Villa 2005[65]	No	No	Yes	Protocol 007. Safety/tolerability: same data as Villa 2006, less detailed
Garland[63]	Yes	No	Yes	Protocol 013, 3 years follow-up
Future II study group[39]	Yes	No	Yes	Protocol 015, 3 years follow-up
Garland [141]	No	No	No	Comparison of immunogenicity between monovalent and quadrivalent vaccine
Block 2006[73]	No	Yes	Yes	Also adverse events in young girls and boys.
Reisinger [74]	No	No	Yes	Immunogenicity in pre-adolescent boys and girls at 18 months. Adverse events in young girls and boys
Joura [58]	Yes	No	Yes	Combined analysis 007-013-015 on vulval and vaginal endpoints
Ault[64]	Yes	No	No	Combined analysis of protocols 005,007,013,015 on cervical endpoints.
Cervarix ® bivalent vaccine 16/18				
Harper 2006[67]	Yes	No	Yes	Update of Harper 2004. Efficacy: data given on CIN 2+ but study not powered for this endpoint
Harper 2004[68]	No	No	Yes	Efficacy: data given on CIN 2+ but study not powered for this endpoint

APPENDICES TO CHAPTER ON ECONOMIC LITERATURE (CHAPTER 4)

APPENDIX 1: CLASSIFICATION OF ECONOMIC STUDIES

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">Are both costs (inputs) and consequences (outputs) of the alternatives examined?</td></tr>
<tr><td colspan="2">No</td><td rowspan="2">Yes</td></tr>
<tr><td colspan="2"></td><td>Examines consequences only</td><td>Examines costs only</td></tr>
<tr><td rowspan="5">Is there a comparison of at least two alternatives?</td><td rowspan="2">No</td><td colspan="2">Partial evaluation</td><td>Partial evaluation</td></tr>
<tr><td>Outcome description</td><td>Cost description</td><td>Cost-outcome description</td></tr>
<tr><td rowspan="3">Yes</td><td colspan="2">Partial evaluation</td><td>Full economic evaluation</td></tr>
<tr><td>Efficacy or effectiveness evaluation</td><td>Cost comparison</td><td>Cost-utility analysis (CUA)
Cost-benefit analysis (CBA)
Cost-effectiveness analysis (CEA)
Cost-minimisation analysis (CMA)</td></tr>
<tr><td colspan="4"></td></tr>
</table>

Adapted from Drummond et al.[142]

APPENDIX 2: DATA EXTRACTION SHEETS

<table>
<tr><td>Author</td><td>Sanders and Taira, 2003</td></tr>
<tr><td>Country</td><td>USA</td></tr>
<tr><td>Study type</td><td>CUA</td></tr>
<tr><td>Model</td><td>Static Markov model (1 month cycle) – Adapted from Myers et al., 2000
Cohort size: 1,988,600 (12-year-old girls)
Disease progression stages modelled: HPV infection (high or low-risk), SIL (high-grade, low-grade), cancer
HPV type specific endpoints (high-risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68; and low-risk: all other HPV types)
No herd immunity
No possibility for reactivation of latent infections
No possibility for strain replacement
No possibility for cross-protection
No optimisation of current screening practice
No impact on genital warts</td></tr>
<tr><td>Perspective</td><td>Not stated</td></tr>
<tr><td>Time window</td><td>Lifetime</td></tr>
<tr><td>Interventions</td><td>HPV vaccine</td></tr>
<tr><td>Scenarios</td><td>- Vaccination of 12-year-old girls + current screening practice
- Current screening practice</td></tr>
<tr><td>Assumptions</td><td>VACCINE
Number of doses: 3
Efficacy: 75% against 13 high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) HPV infections
Coverage: 70% (same as coverage HBV vaccine in US)
Efficacy duration: 10 years
Waning of immunity: no
Booster: 1 dose every 10 years</td></tr>
<tr><td></td><td>SCREENING ONLY
Current practice in the USA: screening every 2 years, starting at age 16
Conventional cervical cytological screening
Coverage: 71%
Sensitivity for SIL: 51%
Specificity for SIL: 97%</td></tr>
<tr><td></td><td>SCREENING COMBINED WITH VACCINATION
Same as screening only
No optimal screening scenarios investigated</td></tr>
<tr><td></td><td>HPV RATES
Prevalence of HPV in initial cohort population: 0%
Proportion of high-risk HPV infections: 59%
Annual incidence HPV infection per age:
<table>
<tr><td>Age</td><td>Incidence</td><td>Age</td><td>Incidence</td></tr>
<tr><td>0–15</td><td>0</td><td>21</td><td>0.12</td></tr>
<tr><td>15–16</td><td>0.1</td><td>22–23</td><td>0.10</td></tr>
<tr><td>17</td><td>0.12</td><td>24–29</td><td>0.05</td></tr>
<tr><td>18</td><td>0.15</td><td>30–49</td><td>0.01</td></tr>
<tr><td>19</td><td>0.17</td><td>50+</td><td>0.005</td></tr>
<tr><td>20</td><td>0.15</td><td></td><td></td></tr>
</table>
Annual probability (%) of HPV infection regressing (yrs):
<table>
<tr><td>Age</td><td>Rate</td></tr>
<tr><td>0–24</td><td>45.7</td></tr>
<tr><td>25–29</td><td>32.9</td></tr>
<tr><td>30+</td><td>6.8</td></tr>
</table></td></tr>
<tr><td></td><td>DISEASE PROGRESSION
Disease progression rates partly reported (see article)
Relative progression rates for transition from high-risk, low-risk, or no HPV infection to</td></tr>
</table>

	LSIL; from LSIL to HSIL; and from HSIL to cervical cancer		
	TREATMENT 10% of women with LSIL undergo cryotherapy Women with HSIL undergo loop electrosurgical excision procedure Cone biopsy Women with hysterectomy are fully protected against cervical cancer		
Data source for costs	Costs in 2001 US $ MEDICARE average reimbursement rates Literature: Helms et al, 1999		
Cost items included	Direct medical costs		
Data source for outcomes	Literature QoL from the US Institute of Medicine, 2000 (QALY weights from experts)		
Discounting	Cost: 3% Outcome: 3%		
Costs	INTERVENTIONS HPV vaccination course: $300 (vaccine, personnel and administration) Cytological screening: $81 (including 10% re-screening) Booster course: $100 (vaccine, personnel and administration)		
	TREATMENT LSIL: $630 HSIL: $1,218 Cervical cancer- stage I: $14,979 Cervical cancer – stage II: $21,811 Cervical cancer – stage III: $21,811 Cervical cancer stage IV: $24,004		
	TOTAL COST - LIFETIME		
	Discounted value	*No vaccination*	*HPV vaccination*
		$39,682	$39,928
Outcomes	QALY WEIGHTS Undiagnosed HPV or SIL: 1 SIL: 0.97 Cervical cancer – stage I: 0.79 (during the 4-months of initial treatment), 0.90 (during 2-3 years of follow-up after initial treatment) Cervical cancer – stages II-IV: 0.62 (4-months initial treatment and 2-3 years follow-up) Cervical cancer survivor: 1		
	TOTAL OUTCOME – LIFETIME		
	Discounted values	*No vaccination*	*HPV vaccination*
	LY	28.785	28.793
	QALY	27.720	27.731
	HPV infection	1,684,954	1,460,699
	SIL	530,259	417,549
	Cervical cancer	16,690	13,374
	Cervical-cancer death	6,461	5,121
Cost-effectiveness	Incremental costs: $246 Incremental life expectancy: 2.8 days Incremental QALYs: 4 days ICUR – comparison with current practice: $22,755 / QALY gained ICER – comparison with current practice: $32,066 / LYG		
Sensitivity analysis	Multi-way sensitivity analysis. Varied parameters: lifelong immunity, vaccination age, discount rate (0% and 5%), vaccine efficacy, vaccination cost, screening coverage Results sensitive to: vaccine efficacy duration, lifelong immunity ($12,682 / QALY gained), screening coverage at 100% ($33,218 / QALY gained), discount rate, QOL, HPV incidence, screening frequency Results robust to: vaccine efficacy, vaccination cost (given a $50 000 threshold)		
Conclusions	'HPV vaccination is cost-effective compared to current practice' 'Although gains in life expectancy may be modest at the individual level, population benefits are substantial'		
Remarks	At time of writing this econ eval, only efficacy data from phase I studies is available: Harro et al 2001, Schiller et al 2001.		

Author	**Kulasingam and Myers, 2003**
Country	USA
Study type	CEA
Model	Static Markov model (1 month cycle) – Adapted from Myers et al., 2000 Disease progression stages: HPV infection (high or low-risk), persistent infection, CIN 1, CIN 2-3, cancer HPV type specific endpoints (low and high-risk) No herd immunity No possibility for reactivation of latent infection No impact on genital warts No possibility for strain replacement No possibility for cross protection HPV type specific outcome (limited to high-risk HPV types)
Perspective	Not stated
Time window	Up to 85 years
Interventions	HPV vaccine
Scenarios	- No intervention - Various 'optimal' screening scenarios - Vaccination of 12-year-old girls only - Vaccination of 12-year-old girls + various 'optimal' screening scenarios
Assumptions	VACCINE Number of doses: 3 Efficacy: 90% against 70% of the high-risk HPV infections (including HPV 16/18 types). Coverage: 100% Efficacy duration: 10 years Waning of immunity: yes Booster: No Response rate: 100% Breakthrough infections: no
	SCREENING (current practice) No comparison with current practice in the USA
	SCREENING (optimisation) Coverage: 100% Sensitivity for CIN 2+: 55.6% Specificity for CIN 2+: 95.7% Various 'optimal' screening scenarios investigated: - conventional cytological screening every 1, 2, 3 or 5 years, starting at age 18 - conventional cytological screening every 1 years, starting at age 22 - conventional cytological screening every 2 years, starting at age 24 - conventional cytological screening every 3 years, starting at age 26 - conventional cytological screening every 5 years, starting at age 30
	HPV RATES Prevalence of HPV in initial cohort population: 0% Incidence rate not reported – see however the graphs with the simulated HPV and cervical cancer incidence over time
	DISEASE PROGRESSION Disease progression rates not reported (refers to previous publications) Colposcopy Sensitivity for CIN 2+: 100% Specificity for CIN 2+: 100%
Data source for costs	Costs in 2001 US $ MEDSTAT and MEDICARE data
Cost items included	Direct medical costs Indirect costs in sensitivity analysis
Data source for outcomes	Literature: Kim et al., 2002 and Mandelbiatt et al., 2002
Discounting	Cost: 3% Outcome: 3%

<table>
<tr><td>Costs</td><td>INTERVENTIONS
HPV vaccination course: $200 (including administrations costs)
Cytological screening: $45
Booster course: $200 (in sensitivity analysis)</td></tr>
<tr><td></td><td>TREATMENT
Colposcopy and biopsy: $436
CIN 1: $2010
CIN 2-3: $3546
Cervical cancer – stage I: $20,524
Cervical cancer – stage II-III: $31,485
Cervical cancer – stage IV: $46,851</td></tr>
<tr><td></td><td>INDIRECT COSTS (in sensitivity analysis):
Vaccination time costs: time for 3 office visits for a parent</td></tr>
<tr><td></td><td>TOTAL COST – LIFETIME (Per person)<table><tr><td>Strategy</td><td>Cost (discounted $)</td></tr><tr><td>No intervention</td><td>284</td></tr><tr><td>Screening every 5 y, at age 18</td><td>483</td></tr><tr><td>Screening every 3 y, at age 18</td><td>632</td></tr><tr><td>Screening every 2y, at age 24 + vaccine</td><td>834</td></tr><tr><td>Screening every 2y, at age 18 + vaccine</td><td>973</td></tr></table></td></tr>
<tr><td>Outcomes</td><td>QALY WEIGHTS (in sensitivity analysis)
CIN 1: 0.97 – 1 (for 1 month)
CIN 2-3: 0.93 – 1 (for 1 month)
Cervical cancer – stage I: 0.68 (for the first 5 years of follow-up)
Cervical cancer – stage II-III: 0.56 (for the first 5 years of follow-up)
Cervical cancer – stage IV: 0.48 (for the first 5 years of follow-up)
Cervical cancer survivor (after the first 5 years of follow-up): 1</td></tr>
<tr><td></td><td>TOTAL OUTCOME – LIFETIME (per women)<table><tr><td>Strategy</td><td>Life expectancy (discounted years)</td></tr><tr><td>No intervention</td><td>28.7120</td></tr><tr><td>Screening every 5 y, at age 18</td><td>28.7450</td></tr><tr><td>Screening every 3 y, at age 18</td><td>28.7518</td></tr><tr><td>Screening every 2y, at age 24 + vaccine</td><td>28.7563</td></tr><tr><td>Screening every 2y, at age 18 + vaccine</td><td>28.7578</td></tr></table></td></tr>
<tr><td>Cost-effectiveness</td><td>ICER: comparison with next best alternative (in terms of increased cost), after ruling out cases of dominance and extended dominance:
- Vaccination 12-y girls: extended dominance by screening every 5 y, at age 18
- Screening every 5 y, at age 18: $6,030 / LYG
- Screening every 3 y, at age 18: $21,912 / LYG
- Screening every 2 y, at age 24 + vaccine: $44,889 / LYG
- Screening every 2 y, at age 18 + vaccine: $92,667 / LYG

No ICER reported with utilities ($/QALY) or with inclusion of time costs.</td></tr>
<tr><td>Sensitivity analysis</td><td>Sensitivity analyses performed on strategy ‘vaccine + biennial screening starting at age 24’
1-way and 2-way sensitivity analyses.
Varied parameters: booster, indirect costs, CUA, duration vaccine efficacy, vaccination cost, vaccination age, age at screening initiation, screening interval
No sensitivity analysis on discount rates.
Results sensitive to: vaccine efficacy duration, vaccine efficacy, age at screening initiation, screening interval, if booster at age 22 for an additional 10 years of protection: $77 000 / LYG, vaccine response rate, vaccination age and cost</td></tr>
<tr><td>Conclusions</td><td>‘Screening only is the preferred strategy at less frequent screening intervals (screening every 3, 5 years, starting at 18 years). At more frequent screening intervals, a combination of screening and vaccination is preferred, especially when the start age of screening is delayed.’ ‘Using a $50 000 per LYG as threshold, vaccine + biennial screening starting at age 24 appears to be the most attractive strategy’</td></tr>
<tr><td>Remarks</td><td>At the time of writing, published data on efficacy is only available from protocol 005 of Gardasil (PoC HPV 16), i.e. preliminary data from phase II trial (Koutsky et al, 2002)</td></tr>
</table>

Author	**Goldie et al., 2004**
Country	USA
Study type	CUA
Model	Static markov model (6-months cycle) – Based on Goldie et al., 2003 Hypothetical cohort: 100 000 Disease progression stages: HPV infection (transient low-risk HPV, transient high-risk HPV, persistent low-risk HPV, persistent high-risk non-HPV16/18, persistent high-risk HPV16/18), CIN 1, CIN 2-3, cancer (local, regional, distant) HPV type specific endpoints (low-risk, high-risk 16/18 and high-risk non-16/18) – High-risk HPV types are: 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59 and 68. No herd immunity No impact on genital warts Possibility for reactivation of latent infection Possibility for strain replacement No possibility for cross-protection
Perspective	Societal
Time window	Lifetime
Interventions	HPV 16/18 vaccine
Scenarios	- Current screening practice - Vaccination of 12-year-old girls + current screening practice - Various 'optimal' screening scenarios - Vaccination of 12-year-old girls + various 'optimal' screening scenarios
Assumptions	VACCINE Number of doses: 3 Efficacy: 90% against HPV 16/18 persistent infection Coverage: 100% Efficacy duration: lifelong Waning of immunity: no Booster: no Response rate: 100%
	SCREENING (current practice) Current practice in the USA Initiation age not clearly defined Coverage and periodicity: 5.2% no screening, 70.5% < 1 yr ago, 12.6% < 2 yrs, 4.3% < 3 yrs, 3% < 5 yrs, 9.6% > 5 yrs Liquid-based cervical cytological screening Sensitivity for SIL: 84% Specificity for SIL: 88% Conventional cervical cytological screening Sensitivity for SIL: 66% Specificity for SIL: 97%
	SCREENING (optimisation) Various 'optimal' screening scenarios investigated: Coverage: 100% Conventional or liquid-based cytological screening every 1, 2, 3, 4 or 5 years, starting at ages 18, 21, 25, 30 or 35 years
	HPV RATES Prevalence of HPV in initial cohort population: 0% Annual incidence HPV infection per age:

Age	*Transient HPV*	*Age*	*Persistent HPV*
< 35 y	0.030 – 0.070	< 35 y	0.010 – 0.030
≥ 35 y	0.002 – 0.010	≥ 35 y	0.002 – 0.006

Annual rate of HPV regression:

Age	*Rate*
< 35 y	0.100 – 0.460
≥ 35 y	0.100 – 0.460

	DISEASE PROGRESSION Only women with persistent HPV infection can develop CIN 2,3 and invasive cancer Disease transmission rates partly reported (see article)	
Data source for costs	Costs in 2002 US $ Published literature and MEDICARE data	
Cost items included	Direct medical costs Indirect costs	
Data source for outcomes	Literature QoL: US Institute of Medicine, 2000 – QOL weights from experts	
Discounting	Cost: 3% Outcome: 3%	
Costs	INTERVENTIONS HPV vaccination course: $377 (vaccine: $300 + personnel and administration: $77) Patient time cost for vaccination: $16 Conventional cytology: $15 - $51 Liquid-based cytology: $28 - $64	
	TREATMENT CIN 1: $1,264 CIN 2,3: $2,833 Cervical cancer- stage I: $21,533 Cervical cancer – stage II: $23,046 Cervical cancer – stage III: $27,067 Cervical cancer stage IV: $36,912	
	INDIRECT COSTS: Vaccination time costs: $16 Screening time cost: $21 Transportation costs	
	TOTAL COST – LIFETIME (per women)	
	Strategy (discounted values)	*Cost*
	Current screening	1111
	Current screening + vaccine	1400
	Screening every 5 y, at age 30 + vaccine	748
	Screening every 5 y, at age 25 + vaccine	828
	Screening every 5 y, at age 21 + vaccine	896
	Screening every 3 y, at age 25 + vaccine	1030
Outcomes	QALY WEIGHTS Cervical cancer – stage I: 0.65 (treatment), 0.97 (follow-up after treatment) Cervical cancer – stage II: 0.56 (treatment), 0.90 (follow-up after treatment) Cervical cancer – stage III: 0.56 (treatment), 0.90 (follow-up after treatment) Cervical cancer – stage IV: 0.48 (treatment), 0.62 (follow-up after treatment)	
	TOTAL OUTCOME – LIFETIME (per women)	
	Strategy (discounted values)	*QALYs*
	Current screening	25.9815
	Current screening + vaccine	25.9934
	Screening every 5 y, at age 30 + vaccine	25.9893
	Screening every 5 y, at age 25 + vaccine	25.9919
	Screening every 5 y, at age 21 + vaccine	25.9930
	Screening every 3 y, at age 25 + vaccine	25.9953
Cost-effectiveness	OPTIMAL SCREENING: ICER: comparison with next best alternative (in terms of increased effectiveness), after ruling out cases of dominance and extended dominance: - Screening every 5 y, at age 30 + vaccine: $17,200 / QALY - Screening every 5 y, at age 25 + vaccine: $31,200 / QALY - Screening every 5 y, at age 21 + vaccine: $57,400 / QALY - Screening every 3 y, at age 25 + vaccine: $58,500 / QALY CURRENT SCREENING: ICER: comparison with current screening practice: $24,300 / QALY gained	
Sensitivity	1-way sensitivity analysis	

analysis	Varied parameters: Vaccination age, age at screening initiation, screening interval, duration vaccine efficacy, natural history of HPV infection No sensitivity analysis on discount rates Results sensitive to: vaccine efficacy duration, screening initiation age, screening interval, screening coverage Results robust to: vaccine efficacy, vaccine cost (given €50 000 threshold)
Conclusions	'The best balance between costs and benefits appears to be triennial screening starting at age 25 with vaccination at age 12'
Remarks	At the time of writing, published data on efficacy is only available from protocol 005 of Gardasil (PoC HPV 16), i.e. preliminary data from phase II trial (Koutsky et al., 2002)

Author	**Taira et al., 2004**
Country	USA
Study type	CUA
Model	Hybrid model (dynamic / Markov) – Adapted from Myers et al., 2000 Cohort size: 2 000 000 (12-year-old girls) Disease progression stages: HPV infection, SIL (high-grade, low-grade), cancer Modelisation of HPV types 16 and 18 only HPV type specific endpoints (HPV types 16 and 18) Herd immunity included No possibility for reactivation of latent infections No impact on genital warts No possibility for strain replacement No possibility for cross-protection
Perspective	Not stated
Time window	Up to 50-year-old
Interventions	HPV 16/18 vaccine
Scenarios	- Vaccination of 12-year-old girls and boys + current screening practice - Vaccination of 12-year-old girls + current screening practice - Current screening practice
Assumptions	VACCINE Number of doses: 3 Efficacy: 90% against HPV 16/18 infections. Coverage: 70% Efficacy duration: 10 years Waning of immunity: yes Booster: 1 dose every 10 years
	SCREENING (current practice) Current practice in the USA: screening every 2 year, starting at age 16 Conventional cervical cytological screening Coverage: 71% Sensitivity for SIL: 51% Specificity for SIL: 97%
	SCREENING (optimisation) No optimal screening scenarios investigated
	HPV RATES Prevalence of HPV in initial cohort population (12-18 yrs):

	HPV 16	*HPV 18*
Female	2.6%	0.9%
Male	3.5%	1.2%

Annual probability (%) of HPV infection completely regressing (yrs):

Age	*Rate*
12–23	49
24–29	33
30-50	7

DISEASE PROGRESSION Disease progression rates estimated from the literature but not reported
Data source for costs	Costs in 2001 US $
Cost items included	Direct medical costs
Data source for outcomes	Literature Qol: US Institute of Medicine, 2000 – QOL weights from experts
Discounting	Cost: 3% Outcome: 3%
Costs	INTERVENTIONS HPV vaccination course: $300 (vaccine, personnel and administration)

<table>
<tr><td></td><td colspan="4">Cytological screening: $81 (including 10% re-screening)
Booster course: $100 (vaccine, personnel and administration)</td></tr>
<tr><td rowspan="5">Outcomes</td><td colspan="4">QALY WEIGHTS:
Not reported</td></tr>
<tr><td colspan="4">TOTAL OUTCOME – LIFETIME</td></tr>
<tr><td>Discounted values</td><td>Current screening</td><td>Current screening + vaccination of girls</td><td>Current screening + vaccination of girls and boys</td></tr>
<tr><td>HPV16/18 cancer</td><td>9,147</td><td>422</td><td>113</td></tr>
<tr><td>LY</td><td>28.7975</td><td>28.8112</td><td>28.8117</td></tr>
<tr><td></td><td>QALY</td><td>27.7422</td><td>27.7590</td><td>27.7596</td></tr>
<tr><td>Cost-effectiveness</td><td colspan="4">Vaccination of girls + current screening versus current screening:
Incremental costs: $244 (per women)
Incremental life expectancy: 5.0 days
Incremental QALYs: 6.1 days
ICUR: $14,583 / QALY gained
ICER: $17,802 / LYG
Vaccination of girls & boys + current screening versus vaccination of girls + current screening:
Incremental costs: $261 (per women)
Incremental life expectancy: 0.18 days
Incremental QALYs: 0.21 days
ICUR: $442,039 / QALY gained
ICER: $534,317 / LYG</td></tr>
<tr><td>Sensitivity analysis</td><td colspan="4">1-way sensitivity analysis
Varied parameters: vaccination coverage, vaccination age, no booster and waning of immunity
No sensitivity on discount rate
Results sensitive to: vaccine efficacy duration, vaccine coverage (girls and boys vaccination), vaccination age, screening frequency
Results robust to: vaccine efficacy, vaccine coverage (girls only)</td></tr>
<tr><td>Conclusions</td><td colspan="4">‘Male vaccination may not be the most cost-effective public health strategy’ ‘If waning of immunity or low coverage rate, male vaccination becomes attractive’ ‘If the screening frequency associated with female vaccination is only performed every 3 years (or less), female vaccination become dominant versus current practice’</td></tr>
<tr><td>Remarks</td><td colspan="4">At the time of writing, published data on efficacy is only available from protocol 005 of Gardasil (PoC HPV 16), i.e. preliminary data from phase II trial (Koutsky et al, 2002)</td></tr>
</table>

Author	**Elbasha, Dasbach and Insinga, 2007**
Country	USA
Study type	CUA
Model	Dynamic model Disease progression stages: HPV infection, CIN 1, CIN 2, CIN 3, cervical cancer and genital warts HPV types specific endpoints (HPV 6/11,16/18 infections and diseases) Type-specific disease progression stage (HPV 16/18 vs HPV 6/11) Assumes type-specific lifetime immunity after natural HPV infection (SIR) Includes herd immunity Includes impact on genital warts No possibility for strain replacement No possibility for strain cross-protection Possibility of breakthrough infection
Perspective	Not stated
Time window	100 years (=lifelong)
Interventions	HPV 6,11,16,18 vaccine
Scenarios	- Vaccination of 12-year-old girls + current screening (F12) - Vaccination of 12-year-old girls and boys + current screening (F&M12) - Vaccination of 12-year-old girls and catch-up female 12-24 years old + current screening (F12 + CU-F) - Vaccination of 12-year-old girls and boys and catch-up female 12-24 years old + current screening (F&M12 + CU-F) - Vaccination of 12-year-old girls and boys and catch-up female and male 12-24 years old + current screening (F&M12 + CU-F&M) - Current screening practice
Assumptions	VACCINE (routine vaccination) Number of doses: 3 (in 70% of 12-year-old recipients) Efficacy: 90% against HPV 6/11/16/18 infections 100% against HPV 6/11/16/18 associated disease Coverage: gradual increase during 5 years then 70% Efficacy duration: lifelong Waning of immunity: no Breakthrough infection: yes
	VACCINE (catch-up vaccination) Catch-up duration: 5 years Number of doses: 3 Efficacy: 90% against HPV 6/11/16/18 infections 100% against HPV 6/11/16/18 associated disease 0% in recipients already infected with HPV 6/11/16/18 Coverage: gradual increase up to 50% in year 5. Efficacy duration: lifelong Waning of immunity: no
	SCREENING (current practice) Current practice in the USA (not clearly defined however) Liquid-based cervical cytological screening Coverage: age-dependant Sensitivity: NS Specificity: 94%
	SCREENING (optimisation) No optimal screening scenarios investigated
	TREATMENT Colposcopy Sensitivity: 96% Specificity: 48%
	REPORTED RATES (in tables in appendixes): Disease progression rates in the presence of HPV 16/18 and HPV 6/11

<table>
<tr><td></td><td>Disease regression rate in the presence of HPV 16/18 and HPV 6/11
Cervical cancer mortality rates (age and state dependent)
Hysterectomy rates
Cervical cytology screening rates</td></tr>
<tr><td>Data source for costs</td><td>Literature
Costs in 2005 US $</td></tr>
<tr><td>Cost items included</td><td>Direct medical costs</td></tr>
<tr><td>Data source for outcomes</td><td>Literature and expert opinion
Mortality rates: National Cancer Institute
QoL: Myers, 2004 – conference abstract (Patient based Qol);</td></tr>
<tr><td>Discounting</td><td>Cost: 3%
Outcome: 3%</td></tr>
<tr><td>Costs</td><td>INTERVENTIONS:
HPV vaccination course: $360 (vaccine and administration)
Liquid-base cytology screening: $99</td></tr>
<tr><td></td><td>TREATMENT:
Genital warts: $489
Colposcopy and biopsy: $318
CIN 1: $1,554
CIN 2/3: $3,483
Localised cervical cancer: $26,470
Regional cervical cancer: $28,330
Distant cervical cancer: $45,376</td></tr>
<tr><td></td><td>TOTAL COST – LIFETIME (per 100 000 population)
<table><tr><td>Strategy (discounted values)</td><td>Total cost</td></tr><tr><td>Current screening</td><td>$72,659,302</td></tr><tr><td>F12</td><td>$74,042,990</td></tr><tr><td>F&M12</td><td>$78,707,825</td></tr><tr><td>F12 + CU-F</td><td>$74,815,667</td></tr><tr><td>F&M12 + CU-F</td><td>$79,746,357</td></tr><tr><td>F&M12 + CU-F&M</td><td>$81,761,210</td></tr></table></td></tr>
<tr><td>Outcomes</td><td>QALY WEIGHTS
Localised cervical cancer: 0.76 (initial treatment and follow-up)
Regional cervical cancer: 0.67 (initial treatment and follow-up)
Distant cervical cancer: 0.48 (initial treatment and follow-up)
Cervical cancer survivor(all): 0.76
CIN 1: 0.91
CIN 2/3: 0.87
Genital warts: 0.91</td></tr>
<tr><td></td><td>TOTAL OUTCOME – LIFETIME (per 100 000 population)
<table><tr><td>Strategy (discounted values)</td><td>QALYs</td></tr><tr><td>Current screening</td><td>2,698,711</td></tr><tr><td>F12</td><td>2,699,178</td></tr><tr><td>F&M12</td><td>2,699,327</td></tr><tr><td>F12 + CU-F</td><td>2,699,343</td></tr><tr><td>F&M12 + CU-F</td><td>2,699,461</td></tr><tr><td>F&M12 + CU-F&M</td><td>2,699,506</td></tr></table></td></tr>
<tr><td>Cost-effectiveness</td><td>ICER: comparison with next best alternative (in terms of increased effectiveness) after ruling out cases of dominance and extended dominance:
- Vaccination of 12-year-old girls + current screening: $2,964 / QALY
- Vaccination of 12-year-old girls and boys + current screening: dominated
- Vaccination of 12-year-old girls and catch-up female 12-24 years old + current screening: $4,666 / QALY
- Vaccination of 12-year-old girls and boys and catch-up female 12-24 years old + current screening: $41,803
- Vaccination of 12-year-old girls and boys and catch-up female and male 12-24 years old + current screening: $45,056</td></tr>
<tr><td>Sensitivity</td><td>1-way sensitivity analysis:</td></tr>
</table>

analysis	Varied parameters: vaccine parameters (duration of protection, efficacy, coverage, cost and target age), QOL, discounting (1% and 5%), duration natural immunity Results sensitive to: duration of vaccine protection (10 years), vaccination coverage, vaccination costs, QALY weights, discount rate, duration of natural immunity (10 years), age at vaccination Multivariate sensitivity analysis (Worst case: duration of protection = 10 years; vaccine coverage = 50%; health utility for genital warts, CIN 1, 2, 3, and carcinoma in situ (CIS) = 0.97; degree of protection against infection = 75%; and degree of protection against HPV related disease = 85%): - Vaccination of 12-year-old girls and catch-up female 12-24 years old + current screening: $29,053 / QALY - Vaccination of 12-year-old girls and boys and catch-up female and male 12-24 years old + current screening: $124,063
Conclusions	'HPV vaccine programme that targets female adolescents and women (12-24 years) can be cost-effective' 'Male vaccination is more attractive the lower the coverage among girls and women' 'Including men and boy vaccination is the most clinically effective strategy' 'HPV vaccination shift the mean age at infection upwards'
Remarks	At the time of writing, published data on efficacy is available from protocol 005 of Gardasil (PoC HPV 16), i.e. preliminary data from phase II trial (Koutsky et al., 2002). Data are also available from the completed phase II clinical trial (Villa, 2005)

Author	**Neilson and Freisleben de Blasio, 2007**
Country	Norway
Study type	CEA CUA
Model	Dynamic model Based on Garnett et al, 2006 (?) Disease progression stages: HPV infection, CIN 1, CIN 2, CIN 3, cervical cancer stages I to IV HPV type specific endpoints (16,18, 6/11, 10 other high-risk types) Assumes type-specific lifetime immunity after natural HPV infection (SIR)
Perspective	Health care system Society
Time window	Up to 52 years after vaccine introduction (i.e. from 12-yo to 64 yo) Results reported also for 10, 20, 30, 40 and 50 years time horizons
Interventions	HPV 16,18 vaccine
Scenarios	- Vaccination of 12-year-old girls + current screening - Current screening practice
Assumptions	VACCINE (routine vaccination) Number of doses: 3 Efficacy: 90% against HPV 16/18 Coverage: 90% Efficacy duration: 10 years Waning of immunity: yes Booster: 1 vaccine dose after 10 years (at 22 years)
	SCREENING (current practice) Current practice in Norway: screening every 3 years, starting at age 25 (up to 65-year-old) Coverage: 80% Sensitivity for CIN 1: 50% (Personal communication, Neilson) Sensitivity for CIN 2: 63% (Personal communication, Neilson) Sensitivity for CIN 3: 64% (Personal communication, Neilson) Specificity: 90% (Personal communication, Neilson)
	SCREENING (optimisation) No optimal screening scenarios investigated
	HPV rates and disease progression rates not reported.
Data source for costs	Norwegian registry Literature Expert opinion Costs in 2006 NOK
Cost items included	Direct medical costs: screening, diagnostic and therapeutic work of positive screening test results, treatment of pre-cancers and cancers, vaccination costs. Indirect costs: productivity costs (morbidity and mortality time costs) assessed with the human capital approach Travel costs
Data source for outcomes	Systematic review (other HTA report) QALY weights: derived from Goldie et al, 2004, and therefore from the US Institute of Medicine, 2000
Discounting	Cost: 4% Outcome: 4%
Costs	INTERVENTIONS: HPV vaccination course: NOK 2,835 (excluding administration costs and VAT – cost 1 dose of vaccine is NOK 945 without VAT and NOK 1,259.40 with VAT) Total annual cervical cancer screening costs: NOK 183,260 000
	TREATMENT: Total annual workup costs for abnormal findings (diagnostic): NOK 25,525,800 Total annual workup costs for abnormal cytology findings (therapeutic, HSIL-CIN 2/3): NOK 16,530,500 Total annual cancer workup costs (diagnostic): NOK 1,458 000
	INDIRECT COSTS:

	2/3 of women aged 16-74 years were employed in 2005 No leisure time cost to unemployed women Per OP radiotherapy (and/or chemotherapy) session: 2 working hours lost Cost of a working year: NOK 316,800
Outcomes	QALY WEIGHTS: Computed by taking the mid-point of the range reported by Goldie et al., 2004 Cervical cancer – stage I: 0.84 (follow-up after treatment) Cervical cancer – stage II: 0.78 (follow-up after treatment) Cervical cancer – stage III: 0.84 (follow-up after treatment) Cervical cancer – stage IV: 0.62 (follow-up after treatment)
Cost-effectiveness	Results are reported for the whole population simulated (size not reported, we only know that about 1.5 million of 12-year-old girls have been vaccination over a 52 years period). Health care system viewpoint, 52-years time horizon, discounted values: Incremental costs: NOK 1,411,896 000 LYG: 2,962 QALY gained: 3,539 ICER: NOK 477 000 / LYG ICUR: NOK 399 000 / QALY gained Societal viewpoint, 52-years time horizon, discounted values: Incremental costs: NOK 418,310 000 LYG: 2,962 QALY gained: 3,539 ICER: NOK 141 000 / LYG ICUR: NOK 118 000 / QALY gained
Sensitivity analysis	1-way and multi-way sensitivity analyses. Varied parameters: vaccine efficacy, vaccine coverage, vaccination cost, discount rate (3%), time horizon Results sensitive to: all parameters varied Decreasing ICERs the longer the study time horizon
Conclusions	With longer time horizons, HPV vaccination may well be cost-effective. There is still great uncertainty in the model assumptions.
Remarks	Norwegian ICER threshold: NOK 400 000 Source for vaccine efficacy not reported.

APPENDIX TO CHAPTER ON ECONOMIC EVALUTION OF HPV VACCINATION FOR BELGIUM (CHAPTER 5)

Tables used for the construction of the projected yearly costs of the HPV vaccination programme and the three-yearly screening programme (Figure 17 and Figure 18).

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	0	0	0	0	0	0	0	0	0	0	0	0
CIN2+ treatment costs	0	0	0	7.052	14.103	21.152	28.198	35.242	81.003	126.745	172.469	218.173
Cervical cancer treatment costs	0	0	0	0	0	0	0	0	12.878	25.751	38.619	51.482
Total costs per year	*0*	*0*	*0*	*7.052*	*14.103*	*21.152*	*28.198*	*35.242*	*93.881*	*152.497*	*211.088*	*269.655*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	0	0	0	0	0	0	0	0	0	0	7.538.854	7.538.854
Screening costs	0	0	0	0	0	0	0	0	0	0	0	0
CIN2+ treatment costs	0	0	0	4.325	8.649	12.972	17.293	21.613	49.676	77.729	105.770	133.799
Cervical cancer treatment costs	0	0	0	0	0	0	0	0	6.390	12.778	19.163	25.546
Total costs per year	*18.487.836*	*18.487.836*	*18.487.836*	*18.492.160*	*18.496.485*	*18.500.807*	*18.505.129*	*18.509.449*	*18.543.902*	*18.578.343*	*26.151.622*	*26.186.035*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	0	0	0	0	0	0	0	0	0	0	7.538.854	7.538.854
Screening net costs	0	0	0	0	0	0	0	0	0	0	0	0
CIN2+ treatment net costs	0	0	0	-2.727	-5.454	-8.180	-10.905	-13.629	-31.326	-49.016	-66.699	-84.374
Cervical cancer treatment net costs	0	0	0	0	0	0	0	0	-6.488	-12.973	-19.456	-25.936
Total net costs per year	*18.487.836*	*18.487.836*	*18.487.836*	*18.485.108*	*18.482.381*	*18.479.655*	*18.476.930*	*18.474.206*	*18.450.021*	*18.425.846*	*25.940.535*	*25.916.380*

Year	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	0	2.028.687	2.028.687	2.028.687	4.053.262	4.053.262	4.053.262	6.072.520	6.072.520	6.072.520	8.083.232	8.083.232
CIN2+ treatment costs	263.865	338.105	338.105	338.105	560.680	560.680	560.680	796.757	796.757	796.757	1.039.393	1.039.393
Cervical cancer treatment costs	64.341	135.068	205.757	276.396	346.976	417.505	535.530	653.453	771.264	888.958	1.006.539	1.152.626
Total costs per year	*328.206*	*2.501.860*	*2.572.549*	*2.643.188*	*4.960.918*	*5.031.447*	*5.149.472*	*7.522.730*	*7.640.541*	*7.758.235*	*10.129.164*	*10.275.250*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	0	2.023.575	2.023.575	2.023.575	4.043.079	4.043.079	4.043.079	6.056.846	6.056.846	6.056.846	8.064.447	8.064.447
CIN2+ treatment costs	161.821	207.352	207.352	207.352	343.855	343.855	343.855	488.642	488.642	488.642	663.100	663.100
Cervical cancer treatment costs	31.927	67.024	102.105	137.166	172.202	207.216	265.815	324.375	382.889	444.870	506.803	584.395
Total costs per year	*26.220.438*	*28.324.640*	*28.359.721*	*28.394.782*	*30.585.825*	*30.620.839*	*30.679.439*	*32.896.553*	*32.955.067*	*33.017.048*	*35.261.038*	*35.338.630*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	0	-5.112	-5.112	-5.112	-10.183	-10.183	-10.183	-15.673	-15.673	-15.673	-18.785	-18.785
CIN2+ treatment net costs	-102.043	-130.753	-130.753	-130.753	-216.824	-216.824	-216.824	-308.115	-308.115	-308.115	-376.293	-376.293
Cervical cancer treatment net costs	-32.414	-68.045	-103.652	-139.230	-174.774	-210.289	-269.715	-329.078	-388.375	-444.089	-499.736	-568.231
Total net costs per year	*25.892.232*	*25.822.780*	*25.787.173*	*25.751.594*	*25.624.907*	*25.589.392*	*25.529.967*	*25.373.823*	*25.314.526*	*25.258.813*	*25.131.875*	*25.063.381*

Year	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	8.083.232	10.071.041	10.071.041	10.071.041	12.027.125	12.027.125	12.027.125	13.938.610	13.938.610	13.938.610	15.791.316	15.791.316
CIN2+ treatment costs	1.039.393	1.253.052	1.253.052	1.253.052	1.449.800	1.449.800	1.449.800	1.613.256	1.613.256	1.613.256	1.744.923	1.744.923
Cervical cancer treatment costs	1.298.517	1.444.206	1.589.698	1.734.995	1.906.413	2.077.527	2.248.343	2.418.815	2.588.911	2.771.041	2.952.698	3.133.850
Total costs per year	*10.421.141*	*12.768.300*	*12.913.792*	*13.059.089*	*15.383.338*	*15.554.452*	*15.725.268*	*17.970.681*	*18.140.778*	*18.322.907*	*20.488.938*	*20.670.090*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	8.064.447	10.049.599	10.049.599	10.049.599	12.003.766	12.003.766	12.003.766	13.915.629	13.915.629	13.915.629	15.768.700	15.768.700
CIN2+ treatment costs	663.100	828.026	828.026	828.026	979.901	979.901	979.901	1.118.503	1.118.503	1.118.503	1.250.196	1.250.196
Cervical cancer treatment costs	661.901	739.318	816.649	893.893	985.178	1.076.327	1.167.342	1.266.820	1.366.109	1.503.146	1.639.849	1.776.192
Total costs per year	*35.416.137*	*37.643.633*	*37.720.963*	*37.798.208*	*39.995.535*	*40.086.684*	*40.177.699*	*42.327.641*	*42.426.930*	*42.563.967*	*44.685.434*	*44.821.777*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	-18.785	-21.442	-21.442	-21.442	-23.358	-23.358	-23.358	-22.982	-22.982	-22.982	-22.617	-22.617
CIN2+ treatment net costs	-376.293	-425.026	-425.026	-425.026	-469.899	-469.899	-469.899	-494.753	-494.753	-494.753	-494.728	-494.728
Cervical cancer treatment net costs	-636.616	-704.888	-773.050	-841.102	-921.235	-1.001.200	-1.081.001	-1.151.995	-1.222.802	-1.267.895	-1.312.850	-1.357.658
Total net costs per year	*24.994.996*	*24.875.333*	*24.807.172*	*24.739.119*	*24.612.198*	*24.532.232*	*24.452.431*	*24.356.959*	*24.286.152*	*24.241.059*	*24.196.496*	*24.151.687*

Year	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	15.791.316	17.581.171	17.581.171	17.581.171	19.319.729	19.319.729	19.319.729	21.008.212	21.008.212	21.008.212	22.652.251	22.652.251
CIN2+ treatment costs	1.744.923	1.860.334	1.860.334	1.860.334	1.932.533	1.932.533	1.932.533	1.994.711	1.994.711	1.994.711	2.037.630	2.037.630
Cervical cancer treatment costs	3.314.455	3.494.502	3.668.577	3.842.040	4.014.817	4.186.878	4.358.185	4.519.251	4.679.548	4.839.007	4.997.585	5.155.251
Total costs per year	*20.850.695*	*22.936.007*	*23.110.083*	*23.283.546*	*25.267.079*	*25.439.139*	*25.610.446*	*27.522.175*	*27.682.472*	*27.841.931*	*29.687.466*	*29.845.132*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	15.768.700	17.558.908	17.558.908	17.558.908	19.297.807	19.297.807	19.297.807	20.986.624	20.986.624	20.986.624	22.630.987	22.630.987
CIN2+ treatment costs	1.250.196	1.365.629	1.365.629	1.365.629	1.437.842	1.437.842	1.437.842	1.500.033	1.500.033	1.500.033	1.542.960	1.542.960
Cervical cancer treatment costs	1.912.146	2.047.701	2.177.820	2.307.502	2.436.692	2.565.367	2.693.500	2.855.718	3.017.163	3.177.762	3.337.475	3.496.269
Total costs per year	*44.957.731*	*46.998.926*	*47.129.045*	*47.258.728*	*49.199.030*	*49.327.706*	*49.455.839*	*51.369.065*	*51.530.509*	*51.691.109*	*53.538.111*	*53.696.905*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	-22.617	-22.264	-22.264	-22.264	-21.921	-21.921	-21.921	-21.588	-21.588	-21.588	-21.264	-21.264
CIN2+ treatment net costs	-494.728	-494.705	-494.705	-494.705	-494.691	-494.691	-494.691	-494.678	-494.678	-494.678	-494.670	-494.670
Cervical cancer treatment net costs	-1.402.309	-1.446.802	-1.490.758	-1.534.539	-1.578.126	-1.621.511	-1.664.685	-1.663.533	-1.662.385	-1.661.244	-1.660.110	-1.658.982
Total net costs per year	*24.107.036*	*24.062.919*	*24.018.963*	*23.975.182*	*23.931.952*	*23.888.567*	*23.845.392*	*23.846.890*	*23.848.037*	*23.849.178*	*23.850.645*	*23.851.773*

Year	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	22.652.251	24.247.466	24.247.466	24.247.466	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587
CIN2+ treatment costs	2.037.630	2.070.637	2.070.637	2.070.637	2.098.473	2.106.669	2.114.802	2.122.857	2.130.827	2.138.709	2.142.646	2.146.529
Cervical cancer treatment costs	5.298.110	5.440.049	5.581.048	5.721.074	5.860.069	5.988.427	6.115.620	6.241.475	6.365.910	6.488.860	6.602.293	6.714.045
Total costs per year	*29.987.991*	*31.758.152*	*31.899.151*	*32.039.176*	*33.750.129*	*33.886.682*	*34.022.009*	*34.155.918*	*34.288.324*	*34.419.156*	*34.536.525*	*34.652.160*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	22.630.987	24.226.516	24.226.516	24.226.516	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941
CIN2+ treatment costs	1.542.960	1.575.974	1.575.974	1.575.974	1.603.815	1.612.026	1.620.174	1.628.244	1.636.229	1.644.126	1.648.070	1.651.960
Cervical cancer treatment costs	3.640.162	3.783.128	3.925.148	4.066.186	4.206.188	4.335.449	4.463.537	4.590.278	4.715.589	4.839.405	4.953.597	5.066.098
Total costs per year	*53.840.798*	*55.612.307*	*55.754.326*	*55.895.365*	*57.607.633*	*57.745.105*	*57.881.342*	*58.016.152*	*58.149.448*	*58.281.160*	*58.399.297*	*58.515.689*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	-21.264	-20.950	-20.950	-20.950	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646
CIN2+ treatment net costs	-494.670	-494.663	-494.663	-494.663	-494.658	-494.643	-494.628	-494.613	-494.598	-494.583	-494.576	-494.569
Cervical cancer treatment net costs	-1.657.948	-1.656.921	-1.655.901	-1.654.887	-1.653.882	-1.652.978	-1.652.083	-1.651.197	-1.650.321	-1.649.456	-1.648.695	-1.647.946
Total net costs per year	*23.852.807*	*23.854.155*	*23.855.175*	*23.856.188*	*23.857.504*	*23.858.423*	*23.859.333*	*23.860.234*	*23.861.124*	*23.862.004*	*23.862.772*	*23.863.528*

Year	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587
CIN2+ treatment costs	2.150.353	2.154.114	2.157.801	2.159.635	2.161.425	2.163.166	2.164.854	2.166.482	2.167.669	2.168.802	2.169.877	2.170.887
Cervical cancer treatment costs	6.823.974	6.931.869	7.037.539	7.126.641	7.213.447	7.327.239	7.437.267	7.543.226	7.632.056	7.716.607	7.796.454	7.871.259
Total costs per year	*34.765.914*	*34.877.570*	*34.986.927*	*35.077.863*	*35.166.458*	*35.281.992*	*35.393.708*	*35.501.295*	*35.591.312*	*35.676.996*	*35.757.917*	*35.833.733*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941
CIN2+ treatment costs	1.655.792	1.659.559	1.663.253	1.665.090	1.666.883	1.668.628	1.670.319	1.671.950	1.673.139	1.674.274	1.675.351	1.676.363
Cervical cancer treatment costs	5.176.764	5.285.383	5.391.761	5.481.451	5.568.829	5.682.831	5.793.062	5.899.216	5.988.209	6.072.916	6.152.910	6.227.853
Total costs per year	*58.630.186*	*58.742.572*	*58.852.644*	*58.944.171*	*59.033.342*	*59.149.089*	*59.261.011*	*59.368.796*	*59.458.979*	*59.544.821*	*59.625.891*	*59.701.847*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646
CIN2+ treatment net costs	-494.562	-494.555	-494.548	-494.545	-494.541	-494.538	-494.535	-494.532	-494.530	-494.528	-494.526	-494.524
Cervical cancer treatment net costs	-1.647.209	-1.646.486	-1.645.778	-1.645.190	-1.644.618	-1.644.408	-1.644.205	-1.644.010	-1.643.846	-1.643.691	-1.643.544	-1.643.406
Total net costs per year	*23.864.272*	*23.865.002*	*23.865.717*	*23.866.308*	*23.866.884*	*23.867.097*	*23.867.303*	*23.867.501*	*23.867.667*	*23.867.825*	*23.867.974*	*23.868.114*

Year	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090
Screening strategy												
Vaccination costs	0	0	0	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0	0	0	0
Screening costs	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587
CIN2+ treatment costs	2.171.831	2.172.017	2.172.186	2.172.340	2.172.477	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597
Cervical cancer treatment costs	7.940.808	8.007.368	8.067.839	8.122.202	8.170.354	8.212.159	8.247.868	8.277.708	8.302.158	8.321.884	8.337.418	8.349.331
Total costs per year	*35.904.225*	*35.970.972*	*36.031.612*	*36.086.129*	*36.134.417*	*36.176.343*	*36.212.052*	*36.241.892*	*36.266.342*	*36.286.068*	*36.301.601*	*36.313.515*
Screening + vaccination strategy												
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941
CIN2+ treatment costs	1.677.309	1.677.495	1.677.665	1.677.818	1.677.956	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076
Cervical cancer treatment costs	6.297.530	6.364.214	6.424.796	6.479.259	6.527.499	6.569.382	6.605.157	6.635.052	6.659.547	6.679.309	6.694.871	6.706.806
Total costs per year	*59.772.469*	*59.839.338*	*59.900.091*	*59.954.708*	*60.003.085*	*60.045.088*	*60.080.863*	*60.110.758*	*60.135.253*	*60.155.016*	*60.170.578*	*60.182.513*
Net costs												
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646
CIN2+ treatment net costs	-494.522	-494.522	-494.522	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521
Cervical cancer treatment net costs	-1.643.277	-1.643.155	-1.643.043	-1.642.943	-1.642.854	-1.642.777	-1.642.712	-1.642.657	-1.642.612	-1.642.575	-1.642.547	-1.642.525
Total net costs per year	*23.868.244*	*23.868.367*	*23.868.479*	*23.868.579*	*23.868.668*	*23.868.745*	*23.868.811*	*23.868.866*	*23.868.911*	*23.868.947*	*23.868.976*	*23.868.998*

Year	2091	2092	2093	2094	2095	2096	2097	2098	2099
Screening strategy									
Vaccination costs	0	0	0	0	0	0	0	0	0
Booster costs	0	0	0	0	0	0	0	0	0
Screening costs	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587	25.791.587
CIN2+ treatment costs	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597	2.172.597
Cervical cancer treatment costs	8.358.199	8.358.199	8.358.199	8.358.199	8.358.199	8.358.199	8.358.199	8.358.199	8.358.199
Total costs per year	*36.322.382*	*36.322.382*	*36.322.382*	*36.322.382*	*36.322.382*	*36.322.382*	*36.322.382*	*36.322.382*	*36.322.382*
Screening + vaccination strategy									
Vaccination costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening costs	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941	25.770.941
CIN2+ treatment costs	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076	1.678.076
Cervical cancer treatment costs	6.715.690	6.715.690	6.715.690	6.715.690	6.715.690	6.715.690	6.715.690	6.715.690	6.715.690
Total costs per year	*60.191.397*	*60.191.397*	*60.191.397*	*60.191.397*	*60.191.397*	*60.191.397*	*60.191.397*	*60.191.397*	*60.191.397*
Net costs									
Vaccination net costs	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836	18.487.836
Booster net costs	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854	7.538.854
Screening net costs	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646	-20.646
CIN2+ treatment net costs	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521	-494.521
Cervical cancer treatment net costs	-1.642.508	-1.642.508	-1.642.508	-1.642.508	-1.642.508	-1.642.508	-1.642.508	-1.642.508	-1.642.508
Total net costs per year	*23.869.014*	*23.869.014*	*23.869.014*	*23.869.014*	*23.869.014*	*23.869.014*	*23.869.014*	*23.869.014*	*23.869.014*

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