Social value of gender-neutral HPV vaccination in Italy

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Abstract

Over the last decade, the main theme underlying my research in Health Economics has been to estimate how the Value for Money of breakthrough pharmaceutical innovation evolves with the availability of new clinical information.

In 2008, Prof. H. Zur Hausen received the Nobel Prize for discovering the cancerogenic role of HPV that he initially discovered in 1976. Following that, in 1989, Prof. Ian Frazer discovered the HPV vaccine that later in 2006 became available globally. After the introduction of the vaccine, the clinical information concerning the HPV changed considerably. At the time of its introduction, the HPV vaccine was mostly used for the prevention of cervical cancer in women. A few years later, the role of HPV as causative agent of gender-neutral cancers was proved, namely anal, oral and head and neck cancers. In 2015, a new version of the vaccine was introduced, active on a larger number of HPV strains causing malignancies.

The five publications included for examination describe the historical contribution of my research to the assessment of the economic value to the payor (National Health System) of the HPV immunisation following the availability of new clinical information. The setting is constant: the Italian population covered by the NHS. The analytical approach varies according to the availability of new inputs informing the economic models, aimed to demonstrate the match between economic assessment and the availability of new clinical evidence about the HPV immunization.

First, an original Markov model [1] demonstrated that vaccinating adolescent girls against HPV would be beneficial and cost-effective as a public health programme in Italy. To provide inputs to the model relevant to Italy, both terms of the economic assessment were drawn from original NHS data that were used in two publications. Specifically, a standardized time trade-off (TTO) methodology was used [2] to quantify the utility loss in health states affected by HPV- induced pathologies in Italy. On the other hand, an innovative Bound Optimisation Model [3] was developed to determine whether the allocation of resources was efficient for the prevention of HPV induced diseases ex-ante.

The outcomes of the cost-effective analyses [1,2,3] were included in the pricing dossier leading to the initial reimbursement of HPV vaccine in Italy.

Furthermore, the BEST II study [4] evaluated the cost-effectiveness of universal vaccination compared with selective vaccination of 12-year-old girls and the economic impact of immunization on various HPV-induced diseases. In this paper, a dynamic Bayesian Markov model was developed to investigate the transmission of HPV virus in cohorts of females and males. As a result, gender-neutral HPV vaccination was found to be a cost-effective alternative when compared with either cervical cancer screening or female-only vaccination.

Based on this new evidence, the Italian Government was the first among the G8 Countries to extend the HPV national immunisation programme to 12-year- old boys (2017).

Finally, a systematic review of the extant literature [5] showed that the inclusion of additional HPV types in the non-violent (active on nine strains of the virus) vaccine offers a significant potential to expand protection against HPV infection. The study was included in the pricing dossier for the reimbursement of the 9-valent HPV vaccine as a replacement of the currently available quadrivalent formulation

My main contribution to research has been the use of triangulation to augment the internal validity of the outcomes. Triangulation has benefited investigators, methods and data collection. In addition to my contributions to the development of the overarching research plan, I also directly contributed to the research output of each published paper submitted for examination.

My contributions reflect the expected research skills to be demonstrated upon conferment of a Doctoral Degree:

- Review of the literature (Papers 1, 4, 5)
- Formulation of research question (Papers 1, 2, 3, 4, 5)
- Choice of methods (Papers 1, 2, 3, 5)
- Data collection (Papers 1, 3, 5)
- Data analysis (Papers 2, 3, 5)
- Analysis of limitations of the research (Papers 1, 2, 3, 4, 5)
- Conclusions and recommendations (Papers 1, 2, 3, 4, 5)

Publications submitted for examination

The following five published papers have been submitted for examination:

1) **Paper 1: "F.S. Mennini**, P. Giorgi Rossi, F. Palazzo, N. Largeron, Health and economic impact associated with a quadrivalent HPV vaccine in Italy. Gynecologic Oncology · December 2008. DOI: 10.1016/j.ygyno.2008.09.0312)"

2) **Paper 2: "FS Mennini**, D Panatto, A Marcellusi, P Cristoforoni, R De Vincenzo, E Di Capua, G Ferrandina, M Petrillo T Sasso, C Ricci, N Trivellizzi A Capone, G Scambia, and R Gasparini. Time Trade-Off Procedure for Measuring Health Utilities Loss With Human Papillomavirus-Induced Diseases: A Multicenter, Retrospective, Observational Pilot Study in Italy. Clinical Therapeutics/Volume 33, Number 8, 2011 FS"

3) **Paper 3: "FS Mennini**, G Baio, G Montagano, G Cauzillo, F Locuratolo, G Becce, L Gitto, A Marcellusi, P Zweifel, A Capone, G Favato. Governance of preventive Health Intervention and On time Verification of its Efficiency: the GIOVE Study. BMJ Open · March 2012 · DOI: 10.1136/bmjopen-2011-000736"

4) **Paper 4:** "K Haeussler, A Marcellusi, **FS Mennini**, G Favato, M Picardo, G Garganese, M Bononi, S Costa, G Scambi, P Zweifel, A Capone, G Baio. Cost-Effectiveness Analysis of Universal Human Papillomavirus Vaccination Using a Dynamic Bayesian Methodology: The BEST II Study. Value in Health, October 2015. DOI: 10.1016/j.jval.2015.08.010"

5) **Paper 5:** "C. Signorelli, A. Odone, V. Ciorba, P. Cella, R.A. Audisio, A. Lombardi, L. Mariani, **FS. Mennini**, et al., Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence. Epidemiology and Infection, Cambridge University Press, April 2017. doi:10.1017/S0950268817000747 2017"

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Grazie

Key notions

HPV virus: Human papillomavirus (HPV) is the cause of many sexually transmitted infections. The transmission of HPV is mostly through skin-to-skin contact. Over 100 strains of HPV have been identified, 40 of which can affect genitals, mouth or throat.

HPV vaccine: Human papillomavirus (HPV) vaccines prevent from HPV types causing cervical cancer as well as penis, anus, vulva, vagina, and oropharynx cancers. Available vaccines protect against two, four, or nine types of HPV.

HPV vaccination: Like other immunizations preventing viral infections, HPV vaccines stimulate an individual's immune system to produce antibodies and develop adaptive immunity that, in future encounters with HPV, bind to the virus and prevent it from infecting cells.

Selective Vaccination: Selective immunization of a single gender or age group (e.g. 12-year-old girls)

Gender-neutral (universal) vaccination: Free access to immunization which does not discriminate between genders

Health economics: Health economics is an economic discipline concerned with issues related to efficiency, effectiveness, value and behavior in the production and utilisation of health and healthcare.

Cost-effectiveness: The term cost-effectiveness compares the relative costs and outcomes (effects) of different courses of action and has been used to depict the extent to which interventions measure up to what can be considered to represent value for money.

Preface

The main argument here is that Value for Money of breakthrough pharmaceutical innovation changes with the availability of new clinical information. Health Economic evaluations should closely monitor those changes, to capture the full value of pharmaceutical innovation to society.

I was fortunate enough to be involved since the earliest stages in the Health Economic assessment of one of the most innovative breakthroughs of the century: the vaccine for the prevention of HPV virus infections.

After the introduction of the vaccine, the clinical information concerning the HPV changed considerably:

1. At the time of its introduction, the HPV vaccine was mostly used for the prevention of cervical cancer in women;
2. A few years later, the role of HPV as causative agent of gender-neutral cancers was proved, namely anal, oral and head and neck cancers;
3. In 2015, a new version of the vaccine was introduced, active on a larger number of HPV strains causing malignancies.

The publications included for review describe the historical contribution of my research to the assessment of the economic value from the perspective of the payor (National Health System) of the HPV immunisation following the availability of new clinical information. The setting is constant: the Italian population covered by the NHS. The analytical approach varies according to the availability of new inputs informing the economic models. A brief description of the submitted evidence is reported below, with the aim to demonstrate the match between economic assessment and the availability of new clinical evidence about the HPV immunization.

1. Selective immunisation of school-aged girls for the prevention of cervical cancer.
   HPV vaccination in adolescent girls was demonstrated to be a beneficial programme for public health in Italy. This was achieved using an original Markov model [1] that also showed as the vaccination was a cost-effective choice in Italy. To provide inputs to the model relevant to Italy, both terms of the economic assessment were drawn from original NHS data:

- A standardized time trade-off (TTO) procedure was adopted to quantify "utility loss in health states affected by HPV-induced pathologies in Italy" [2];
- An innovative Bound Optimisation Model was developed to determine the "ex-ante efficiency of resources allocated for the prevention of HPV induced diseases"[3].

The outcomes of the cost-effective analysis [1,2,3] were included in the pricing dossier leading to the initial reimbursement of HPV vaccine in Italy.

2. HPV is a gender-neutral killer: cost-effectiveness of vaccinating boys against HPV.

   The BEST II study [4] evaluated both the cost-effectiveness of universal vaccination compared with cervical cancer screening and selective, female-only vaccination and the economic impact of immunization on various HPV-induced diseases. A dynamic Bayesian model investigated the transmission dynamics of HPV in cohorts of females and males. Gender-neutral HPV vaccination was demonstrated to be a cost-effective option when compared with either cervical cancer screening or female-only vaccination.

   Based on this new evidence, the Italian Government was the first among the G8 Countries to extend the HPV national immunisation programme to 12-year- old boys (2017).

3. Cost-effectiveness of the new version of the HPV vaccine.

   A systematic review of the extant literature [5] showed that the inclusion of additional HPV types in the 9-valent vaccine (covering against nine strains of the virus) offers a remarkable potential to expand protection against HPV infection.

   The study was included in the pricing dossier for the reimbursement of the 9-valent HPV vaccine as a replacement of the currently available quadrivalent formulation

Common to all Health Economics studies, the publications included for review show several Authors: this is due to the different expertise required to validate the inputs relevant to the models: economic, statistical, epidemiological, clinical. In any project, though, I had a leading role in the health economic assessment. A detailed list of my contribution to each publication is reported in the annotated summary of relevant publication.

Synthesis

Significance

This thesis aims to demonstrate how the Value for Money of breakthrough pharmaceutical innovation changes with the availability of new clinical information. Health Economic evaluations should closely monitor those changes, to capture the full value of pharmaceutical innovation to society.

This thesis provides an evidence-based contribution to the evolutionary governance theory [1]. From the perspective of the National Health System, it is uneasy to detect whether a change constitutes a real innovation. Changes take place continuously, in adaptation to the environment. Innovation could be seen as an important discontinuity from the past, which can take place as a sudden change, a step-wise change or a gradual change, although these labels have little theoretical relevance. What it matters is that the only mode of operating for social systems, such as the NHS, is the continuous evaluation of new information related to the observed impact of innovation on the society. The autopoiesis of social system is the continuous reassessment of previous information on the basis of new ones. Innovation, in this account, can only be an ex-post account: "a retrospective observation in which an event is defined as something innovative or transformative" [2].

In healthcare, evidence generation is often not conducive to assessing real-world innovations in a timely way, particularly where there is a focus on cost-effectiveness [3].

The case of HPV vaccination is iconic in this respect.

The discovery and development of human papillomavirus (HPV) vaccines, which prevent a range of HPV-related cancers, is a truly impressive scientific achievement. In the decade since approval of the quadrivalent vaccine for the prevention of HPV types 6, 11, 16, and 18, the vaccine has been shown to be highly effective [4].

Recently, a 9-valent vaccine was approved, which protects against five additional oncogenic HPV types, providing increased protection [5]. The

introduction of this improved vaccine affords the opportunity to undo an unintentional gender bias that has harmed HPV vaccination efforts.

In origin, due to the association with cervical cancer, HPV vaccine trials were primarily based on females and consequently, the vaccine was reasonably approved only for females between 9 and 26 years old. However, this administration schedule also fit within an existing cultural narrative that HPV was a 'woman's problem'. The identification of HPV with females, and its subsequent impact on the setting of primary prevention strategies, was defined as the "feminization of HPV". The process of 'feminization' occurs when an "issue is socially constructed as focused on females, which can impact how issues are perceived by the public and addressed by the government and other organizations" [6].

Therefore, the feminization of HPV was, somehow, the result of an unintended combination between the state of science at that time and our long history of inequality. The choice to allow the vaccine only for females was ascribable to science, politics, economics, and socially constructed beliefs on gender roles. In the forthcoming transition from the quadrivalent to the 9-valent vaccine that will certainly involve a turmoil regarding guidelines, dosage, clinical practice behavior, and health communications, new strategies could correct gender disparities in vaccine delivery.

HPV is not gender-specific. The feminization of HPV is both influenced and complicated by its sexual transmissibility. Before the approval of the HPV vaccine, thanks to the achievements reached by the Papanicolau test screening, the association of HPV with females has contributed to a reduction in morbidity and mortality rates. Yet, the juxtaposition of HPV and female cancers has limited the debate on the prevention of other HPV-related cancers, such as anal and oropharyngeal cancers, which also do not take advantage of routine screenings.

As a result of the delayed diffusion of scientific evidence connecting males, cancers and HPV, vaccine recommendations for males were postponed and were included in separate guidelines. Consequently, unsettling recommendations based on gender and age continue to exist for the HPV vaccine, with a markedly lower uptake among males.

The deeper concern is that the feminization of HPV results in males not benefiting from this vaccine. In fact, low vaccine rates among females (well below the 80-90% coverage required by the herd immunity to have effect), as

well as heteronormative conventions (e.g., ignoring men who have sex with men) have ultimately plagued the hypothesis that having adequate HPV vaccination rates among females would ultimately protect males through herd immunity. Indeed, the introduction of the vaccine for females only, biased the cost-effectiveness question as it had not asked for any other vaccine before. That is, the question was framed as, "is it cost-effective to add male vaccination to existing female vaccination?" rather than, "is it cost-effective to vaccinate both males and females compared to not vaccinating anyone?" The cost-effectiveness controversy around male vaccination is, in part, a result of the lag between female and male licensure. Thus, the diffusion of cost-effectiveness evaluations for males continues to create an unequal approach to vaccine policy.

The last decade of my research work has been entirely dedicated to fill the gap between evidence generation and assessment of the social value of HPV immunisation strategies. The aim was to maximise the access to vaccination, hence reducing inequalities between genders, sexual preferences and behaviors.

The following paragraph will briefly review the extant literature on the social value of gender-neutral HPV vaccination. The following paragraphs will discuss the research approach, methodological options and contributions underpinning the body of publications submitted for assessment.

Review of the published models on the cost-effectiveness of gender-neutral HPV vaccination.

The access to new vaccines against HPV, has led policymakers to take decisions regarding the most cost-effective immunisation strategies required to reduce the burden of HPV infections and associated diseases. The recognition that male HPV infection has a significant impact on the burden of HPV-related diseases justifies the question of whether males should be or not included in the vaccination programme.

Increasing demand for economic and epidemiological studies resulted in the development and publication of complex statistical models looking at the efficacy and cost-effectiveness of the available HPV vaccines, screening programmes and immunisation strategies. However, from the extant literature

emerges that positions on gender-neutral vaccination against HPV (excluding the studies submitted for examination) have been contradictory.

Two studies [7, 8] reported the universal vaccination against HPV as cost-effective. However, as pointed out in many other contributions, a gender-neutral vaccination schedule was also "possibly cost-effective", "secondary to increasing immunisation coverage of women" [9, 10], and ultimately "never cost-effective" according to three studies [11, 12, 13].

The heterogeneity of outcomes observed in the reviewed publications results from the "high degree of sensitivity to boundary conditions and the choice of inputs". Specifically, some factors justified the increase of the incremental cost-effectiveness ratio (ICER) values such as: "the higher vaccine efficacy, duration of protection, cross-protection, duration of immunisation, and observation period". Conversely, ICER values were decreasing when including a "larger set of HPV-induced diseases (such as recurrent respiratory papillomatosis - RPP), lifetime duration of efficacious vaccination (no subsequent 'booster' dose), a reduced number of doses needed to complete immunisation (two versus three) and a lower unit price per vial of the vaccine". Funding might also play a role in the choice of the inputs to inform the economic models.

Therefore, the likelihood of adding boys that is shown by the difference between the observed ICER values and the acceptability threshold (that is usually set at $50,000 or £30,000), may depend on the general effect of the interaction between the various inputs to the model. As an example, the highest ICER (in $2015 values) observed among the studies included in the systematic review was >$200,000. This value was driven by the highest level of immunisation coverage observed in the review (75% of all 12-26-year-old women, a 13-26-year-old women catch-up cohort and 75% of all 12-year-old males), by an elevated (90 to 100%) adherence to a three-dose vaccination schedule, and by a relatively high vaccine price ($128 per vial).

As a consequence of the large variance observed in the use of different economic inputs over the time, the resulted volatility implied in the ICER values suggests the need for an "expiration date" on the validity of the normative outcomes stemming from cost-effectiveness analyses. Economic and demographic inputs, however, are not the only parameters that may be affected by significant changes over time.

Research approach

The main body of my research is driven by a pragmatic approach of mixed methods applied to the assessment of the social value of HPV vaccination strategies. This logic appeared best suited to investigate the variety of inputs and methods that were relevant to inform policy decisions in healthcare, allowing the required freedom in the choice of different quantitative approaches. Each method, though, has its limitations and different techniques can be complementary.

In fact, the way of analysing data, depends on which measures have been employed and how the data have been collected. Qualitative data, however, can be transformed into quantitative values, , by using quality of life questionnaires to elicit utility values, for instance.

Being able to integrate different approaches has the advantages of enabling triangulation [14]. Triangulation is a common feature of mixed methods studies and involves, for example:

- "the use of a variety of data sources (data triangulation)
- the use of several different researchers (investigator triangulation)
- the use of multiple perspectives to interpret the results (theory triangulation)
- the use of multiple methods to study a research problem (methodological triangulation)" [15].

Main research construct: modeling health economic outcomes

Health economic evaluation is a common framework widely adopted for taking policy-oriented decisions about whether particular health technologies represent a cost-effective use of healthcare resources. Typically, the cost-effectiveness of a given set of alternative health technologies requires extensive evidence that is not available from a single source. This decision-analytic framework can be achieved through the use of mathematical modeling that allows the "full range of relevant evidence to be synthesised and brought to bear on the decision problem" [16]. To develop a decision-analytic model an iterative process is generally required in which the developer has to make some choices to define the inclusion criteria and how these phenomena should be related to one another. These choices take place at every stage of the model development.

They include the selection of the appropriate comparators, the health states and sequences of events that will influence the model's structure, and choices of statistical methods required for deriving the model's parameters. Importantly the absence of perfect information for the validation of a model reflects that there is rarely a definitive means through which determine whether these choices are right or wrong. Instead, choices in models development are made from subjective judgments, with the ultimate aim of developing a model which will be useful to inform the decision maker.

Based on these theoretical premises, the main construct underlying my research is the development of conceptual modeling [17], Figure 1.

Figure 1: Schematic representation of Chilcott's development of conceptual modeling in healthcare
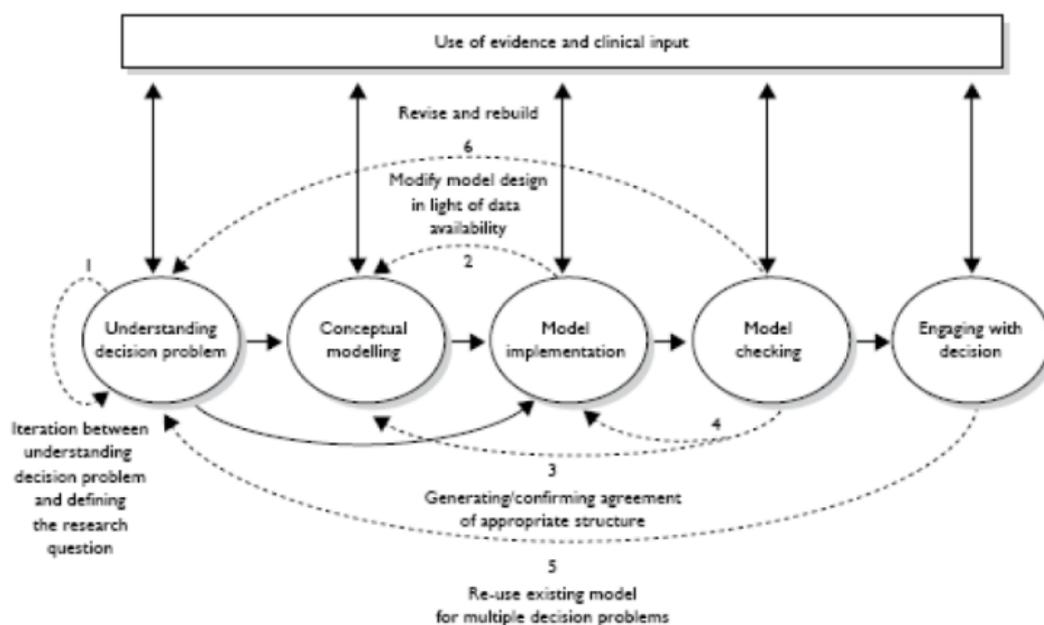
Source: 17.   Chilcott JB, Tappenden P, Rawdin A, Johnson M, Kaltenthaler E, Papaioannou D et al. Avoiding and identifying errors in health technology assessment models. Health Technology Assessment 2009; 14(25):i-135

The main stages in the model development follow both a sequential and iterative flow:

1. Understanding the decision problem: at this initial stage the main activities entail the immersion in research evidence to define the research question. This can also be achieved by engaging with clinicians, decision-makers and methodologists, with the objective of understanding what is feasible.

2. Conceptual modelling: once the gap has been identified, it is necessary to "translate the understanding of the decision problem towards a mathematical or technical model-based solution" [18].

3. Model implementation: then, the implementation of the model is obtained through the use of a software platform.

4. Model checking: this is required to avoid model errors and includes the engagement with experts, the check of face validity, testing values, structure and logic, checking data sources etc.

5. Engaging with decision: in conclusion the model and the results obtained must be made accessible by the decision-makers through an appropriate reporting.

Methods

The five published papers included in this thesis were designed to fill voids in current research into the social value of HPV vaccination in Italy from the perspective of the Italian NHS. They were targeted at proving the main argument of my research that the Value for Money of breakthrough pharmaceutical innovation changes with the availability of new clinical information. Health Economic evaluations should closely monitor those changes, to capture the full value of pharmaceutical innovation to society.

Within all five papers, the social value of HPV immunisation was approached from diverse settings (Table 1). The aim that stands behind the use of this methods is to capture a holistic picture of 'Value in Health', with the intention that the adoption of different perspectives would reveal some elements that do not fit a previous understanding, and that divergent results would promote a "deeper, more complex and less evident explanations" [19, 20]. One goal has been to "choose methods that complement each other and thus increase the validity of the findings" [21, 22]. Not only methodological triangulation, but also "investigator, theory and data triangulation" [23] has been addressed in these studies.

Table 1: Methodological overview of the papers included in the thesis

Paper	Main research question	Research strategy	Data collection method	Analysis method
1. *Health and economic impact associated with a quadrivalent HPV vaccine in Italy.*	To determine the health impact of introducing an HPV vaccination alongside the existing cervical cancer screening programme in Italy.	Cost-effectiveness analysis: a static Markov model based on Us data was adapted to the Italian context.	Italian epidemiological data from published literature were used to inform the model. Then a hierarchical approach was used to fit the HPV prevalence rate	Incremental Cost Effectiveness Ratio (ICER)
2. *Time Trade-Off Procedure for Measuring Health Utilities Loss With Human Papillomavirus-Induced Diseases: A Multicentre, Retrospective, Observational Pilot Study in Italy.*	To investigate the impact of a standardized time trade-off (TTO) procedure on utilities loss in health states affected by HPV-related diseases in Italy.	Multicentre, retrospective, observational, cross-sectional study	European Quality of Life–5 Dimensions (EQ-5D) questionnaire	Spearman rank correlation coefficient
3. *Governance of preventive Health Intervention and On time Verification of its Efficiency: the GIOVE Study.*	To assess the achievement of allocative efficiency of the budget allocated to the prevention of human papillomavirus (HPV)-induced diseases.	A bound optimisation model was developed to determine the ex-ante allocative efficiency of resources.	Real World data from the Basilicata Region: 12 848 girls aged 12, 15, 18 or 25 years	Given the budgetary constraints, the vaccination coverage rate was considered an indicator of the possible benefits.
4. *Analysis of Universal Human Papillomavirus*	To evaluate whether female-only vaccination or	A dynamic Bayesian Markov model was designed	Inputs from published literature and	All parameters were given suitable

Vaccination Using a Dynamic Bayesian Methodology: The BEST II Study	universal vaccination is the most cost-effective intervention against HPV.	to investigate transmission dynamics in cohorts of females and males in a follow-up period of 55years.	clinicians' consensus	probability distributions
5. *Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence.*	To systematically retrieve all available evidence on 9vHPV from randomized controlled trials	Systematic review	Randomised controlled clinical on 9vHPV vaccine	Ten publications reported on RCTs' results on 9vHPV and were included in the review".

The main methodological choices underpinning the research are briefly described below.

Paper 1:

Markov static model	Markov models are frequently used to evaluate the cost-effectiveness of a one-time decision (e.g. vaccinate or not to vaccinate) under resource constraints. Models with embedded decisions as observed in sequential decision problems cannot be practically solved using Markov models. Markov decision processes (MDPs) are analytical tools used for sequential decision making under uncertainty [24].

Paper 2:

Time Trade-Off (TTO):	TTO is widely used to value health states, however, there are some limitations. For example, when people are asked to consider very poor states of health – persistent extreme pain, for example – they may dislike them so much that they would trade off all their time in full health. In other words, they would prefer to be dead. This is called a health "state worse than death" (SWD) [25].

Paper 3:

Bound optimisation:	Bound constrained optimizations are problems entailing the optimization of an objective function that is subject to bound constraints on the values of the variables. Bound constrained optimization problems also arise when "the parameters that describe physical quantities are constrained to be in a given range" [26].

Paper 4:

Bayesian models	Bayesian analysis refers to a different approach to statistical inference in which the purpose of collecting new data is to refine the estimate of a particular quantity (often a probability) that may be used for decision-making. This contrasts with traditional

'frequentist' statistics where data are collected to reject or confirm a null hypothesis at a given level of statistical significance. More specifically, Bayesian techniques are used to "synthesize information known about a parameter before conducting a study with new data from the study to estimate a 'posterior' distribution for that parameter" [27].

Cost-effectiveness   analysis compares the costs and health effects of an intervention to assess its "value for money". This approach is used to assist decision-makers in allocating limited healthcare resources [28].
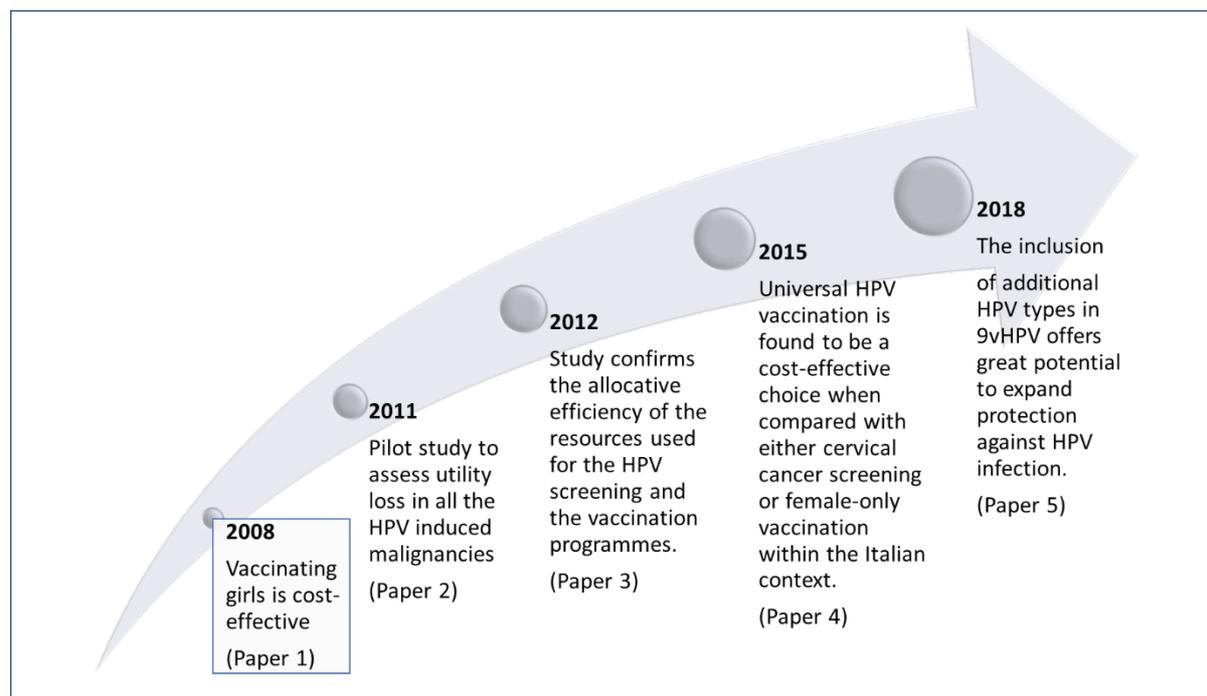
Paper 5:

Systematic review   The objective of systematic reviews is to identify, critically evaluate and integrate the findings of relevant, high-quality individual studies related to one or more research questions. A systematic review is therefore a "piece of research in its own right and, by its nature, can address much broader questions than single empirical studies ever can (e.g. uncovering connections among many empirical findings)" [29].

Outcomes

The development of new valuation perspectives in response to new relevant inputs (both clinical and economical) lead over time to a significant change in the social value of HPV vaccination, as illustrated in Figure 2.

This approach is consistent with the main construct underpinning my research: pragmatism appeared best suited to research the variety of inputs relevant to inform policy decisions in Public Health, such as the optimal immunisation strategy to eradicate HPV. By allowing the freedom to use any of the methods, techniques and procedures typically associated with quantitative research, the policy recommendation moved away from the initial selective strategy (vaccinating 12-year-old girls only) to recognising the social value of gender-neutral immunisation as soon as new inputs relevant to inform the quantitative decision model (cost-effectiveness analysis) became available.

Figure 2: Timeline of main research outcomes and policy recommendations.

2008

Vaccinating girls is cost-effective

(Paper 1)

2011

Pilot study to assess utility loss in all the HPV induced malignancies

(Paper 2)

2012

Study confirms the allocative efficiency of the resources used for the HPV screening and the vaccination programmes.

(Paper 3)

2015

Universal HPV vaccination is found to be a cost-effective choice when compared with either cervical cancer screening or female-only vaccination within the Italian context.

(Paper 4)

2018

The inclusion of additional HPV types in 9vHPV offers great potential to expand protection against HPV infection.

(Paper 5)

The first published paper dates to 2008, which is when the quadrivalent vaccine was just made available in Italy. Accordingly, the objective of the study was to determine the health impact and cost-effectiveness of introducing a quadrivalent vaccine in addition to the existing screening programme for the

prevention of cervical cancer that was the main indication approved. In this study, through the adoption of a static Markov model two scenarios were compared:

• screen against cervical cancer (current context),

• HPV vaccination with a quadrivalent vaccine in association with the existing cervical cancer screening programme provided in Italy.

As a result, the introduction of a quadrivalent vaccine would provide substantial health benefits to the Italian population. Precisely, "the implementation of HPV vaccination among a cohort of girls aged 12 years would avoid 1,432 incremental cases of cervical cancer (−63.3%) and 513 related deaths (−63.4%) compared to screening programme only". This was obtained assuming a coverage rate of 80% and lifetime duration of protection as well as discount rates of 1.5% and 3% for health benefits and costs respectively. Furthermore, this new preventive strategy was reported to be a "cost-effective public health programme, as the cost per additional QALY gained reached €9,569, which is considered as an acceptable threshold" [30].

This relatively simple model had iconic importance in the history of HPV vaccinations. Published almost simultaneously with this study, a cost-effectiveness analysis conducted by Public Health England made the same recommendations for the HPV vaccination in England [31]. The cost-effectiveness outcomes have been confirmed by hundreds of studies published in the extant literature, employing a variety of sophisticated methodologies. The selective vaccination of 12-year-old girls rapidly became the preferred HPV immunisation strategy in Europe and most Countries with a public NHS.

In the following years, Papers 2 and 3 focused on methodological issues related to the valuation of all the HPV-induced malignancies, regardless of the gender.

Paper 2 was a pilot study, aimed to investigate the "feasibility of a standardized time trade-off (TTO) procedure to quantify utility loss in health states affected by HPV-induced pathologies in Italy". A TTO standardized procedure is expected to be useful to assess utilities in patients affected by HPV-induced diseases.

Paper 3 was concerned with another critical aspect of cost-effectiveness analysis of vaccination: the optimal coverage rate. The vaccination coverage rate was the indicator of the best possible benefit, given the budgetary constraints.

At a market-based price per vial of the vaccine, the optimal rate of coverage was in favour of the multiple cohort strategy of vaccination against HPV.

This observation had an extraordinary impact on the development of cost-effectiveness of HPV vaccination: if, give a vaccine price, the optimal coverage is a multi-cohort strategy, what would be the economic impact to add boys to the vaccination of girls?

Paper 4 provided an answer to this novel research question. The sophisticated dynamic Bayesian model suggested for the first time that universal vaccination targeting the same age group (12years) was an extremely cost-effective strategy in comparison to screening-only or to a single cohort of females. The following four innovative aspects determined the outcomes of the study:

1. The dynamic force of infection, including sexual mating between females and males, thus automatically considering changes in mixing patterns and population prevalence over time.

2. The assumption of lifelong immunity following initial HPV vaccination with three doses, without the necessity of a booster application;

3. The considerably low unit cost of vaccination compared with the official list price of the vaccine in the Italian market;

and, most important,

4. The inclusion of a high variety of HPV-induced diseases compared with other health-economic evaluations that account only for cervical cancer.

The last observation served as the foundation for Paper 5, aimed to "systematically retrieve, qualitatively and quantitatively pool, as well as critically appraise all available evidence on 9vHPV from randomized controlled trials (RCTs)". In this paper, we conducted a systematic review of the extant literature on 9vHPV efficacy, immunogenicity and safety, as well as a systematic search of registered, completed, and ongoing RCTs. In this work we followed the review method named PRISMA (Prepared Items for Systematic Reviews and Meta-Analysis) and the related guidelines [22].

The conclusions of the systematic review of the extant clinical literature highlighted as the inclusion of additional HPV types in the vaccine offered great potential to expand protection against HPV infection and the associated burden of diseases. However, the 9vHPV impact in reducing the global burden of HPV-

related cancer was depending on the vaccine uptake and coverage, as well as the availability, and – finally – its affordability from the perspective of the payer.

The conclusions set the stage for a new wave of cost-effectiveness analysis of the new generation of 9-valent vaccine, aiming to assess the social value of this innovative approach to HPV vaccination strategy.

The outcomes of the submitted body of research established the cost-effectiveness of the selective HPV vaccination, posed new, fundamental question on how the value for money was assessed, recognised the necessity of a gender-neutral, universal vaccination and clarified the premises for the adoption of a new generation of vaccines, active on a broader spectrum of HPV oncogenic strains.

By integrating new information into progressively more sophisticated models, the research questions anticipated the development of new and more cost-effective HPV immunisation strategies, providing a substantive contribution to the field of valuation of the social value of pharmaceutical innovation.

Limitations of research outputs

The cost-effectiveness models (Paper 1 and 4) submitted for examination do not address the issue of equality in Public Health raised by a selective (girls-only) vaccination strategy. The principle of equity and equal access to healthcare to maximize a population's health is a cornerstone for all health systems. Therefore the universal vaccination would give men and women the same rights to protection and would:

- protect females and males against many HPV-related diseases such as cervical, vulvar, vaginal and anal (pre) cancers, and genital warts and significantly reduce the remaining burden in both genders;
- improve the control of HPV vaccine types circulation and related diseases and this would potentially lead the "quasi-elimination of vaccine".
- lead HPV vaccination to become a standard vaccination schedule in pre-adolescents;
- reduce gender and social health inequalities by protecting men against unvaccinated female or male partners (increased risk

with population movements) and protecting the most vulnerable people through the prevention of genital warts.

A second limitation is related to the choice of cost inputs that was made to inform the models. This was limited by the perspective of valuation (the NHS system) and by choice of including direct costs only. The full economic benefits of HPV vaccination are difficult to be quantified in monetary terms, unless all indirect costs are included in the analysis (e.g.: decrease of the burden for the caregiver, psychosocial impact, impact on fertility, productivity loss). Consequently, based on existing guidelines, the cost-effectiveness is unlikely to be the most relevant measure for the assessment of the broad social value of HPV gender-neutral vaccination.

Research quality and relevance

Impact factor

The impact factor (IF) is a measure of the number of citations received by a paper published in a particular year. It is used to measure the academic relevance of a journal by calculating the times the articles are cited.

It is commonly adopted as an indirect quality of the papers published, since the acceptance for publication process is generally more difficult and selective the higher the IF of the Journal [32].

The IF of the five published papers submitted was included between 2.2 <>3.8.

- Paper 1: **IMPACT FACTOR: 3.774**

- Paper 2: **IMPACT FACTOR: 2.731**

- Paper 3: **IMPACT FACTOR: 2.271**

- Paper 4: **IMPACT FACTOR: 3.824**

- Paper 5: **IMPACT FACTOR: 2.515**

Citations

Citation analysis is a second approach that is adopted to measure the relative impact of an author, an article or a publication. It consists of "counting the number of times an author, article, or a publication has been cited by other published works" [33].

The five papers submitted for examination have been cited 70 times in similar publications (source: ResearchGate and PubMed).

- Paper 1: **CITATIONS: 51**

- Paper 2: **CITATIONS: 5**

- Paper 3: **CITATIONS: 2**

- Paper 4: **CITATIONS: 7**

- Paper 5: **CITATION: 5**

Personal contribution to research

1. Triangulation

In the body of research submitted for examination, I explored some of the key considerations of data analysis and interpretation for a complex evaluation. The synthesis among multiple and complementary sources is vital to produce credible evidence for policy recommendations in the healthcare sector. Therefore, triangulation refers to the use of multiple sources of qualitative and quantitative information, data collection and analysis methods for obtaining valuable and complex findings or conclusions. The adoption of triangulation can strengthen the quality and credibility of the evidentiary support for findings and recommendations, especially in the complex field of analysis such as the healthcare where any single data source will have inherent limitations. Triangulation has benefited investigators, methods and data collection.

1.1 Investigator triangulation

My contribution to the triangulation of expertise was based on my personal experience in the field of valuation, with specific reference to the assessment of the social value of HPV immunisation strategies,

My academic leadership and experience in the economics of HPV vaccination can be comparatively assessed by ranking the Authors of similar publications in bibliometric databases. My name (10 papers) is listed among the Top 10 most published Authors of HPV studies at a global level (source: Web of Science, 2018).

☐ KIM JJ (24)	☐ LAPRISE JF (7)	☐ BOGAARDS JA (5)	☐ BURGER EA (4)
☐ LARGERON N (22)	☐ OSTENSSON E (7)	☐ BOSCH FX (5)	☐ CHOI YH (4)
☐ GOLDIE SJ (18)	☐ SIEBERT U (7)	☐ DAEMEN T (5)	☐ COUPE VMH (4)
☐ JIT M (14)	☐ ZHAO FH (7)	☐ DIAZ M (5)	☐ DASBACH E (4)
☐ BRISSON M (11)	☐ BENARD S (6)	☐ DROLET M (5)	☐ GARGANESE G (4)
☐ CHESSON HW (11)	☐ BOILY MC (6)	☐ EDMUNDS WJ (5)	☐ KRISTIANSEN IS (4)
☐ POSTMA MJ (11)	☐ CAMPOS NG (6)	☐ KIM J (5)	☐ LEVIN A (4)
☐ CASTLE PE (10)	☐ CAPONE A (6)	☐ KULKARNI AS (5)	☐ MYERS E (4)
☐ DEMARTEAU N (10)	☐ EKWUEME DU (6)	☐ LEGOOD R (5)	☐ O'MAHONY JF (4)
☐ HUTUBESSY R (10)	☐ ELBASHA EH (6)	☐ LEW JB (5)	☐ OLSEN J (4)
☐ MENNINI FS (10)	☐ HABBEMA JDF (6)	☐ LI X (5)	☐ POULIOS N (4)
☐ DE KOK IMCM (9)	☐ HAVANOND P (6)	☐ MARCELLUSI A (5)	☐ PWU RF (4)
☐ MARKOWITZ LE (9)	☐ HILLEMANNS P (6)	☐ O'SHEA M (5)	☐ RESCH S (4)
☐ VAN BALLEGOOIJEN M (9)	☐ JERONIMO J (6)	☐ ORTENDAHL J (5)	☐ SARAIYA M (4)
☐ BAIO G (8)	☐ KHEMAPECH N (6)	☐ PICARDO M (5)	☐ SCAMBIA G (4)
☐ FAVATO G (8)	☐ KULASINGAM S (6)	☐ SHCHEPROV A (5)	☐ SINGHAL PK (4)
☐ INSINGA RP (8)	☐ MEIJER CJLM (6)	☐ SROCZYNSKI G (5)	☐ SMITH M (4)
☐ MYERS ER (8)	☐ PETRY KU (6)	☐ SY S (5)	☐ TANEEPANICHSKUL S (4)
☐ PILLSBURY M (8)	☐ QIAO YL (6)	☐ TAY SK (5)	☐ TANG CH (4)
☐ VAN KRIEKINGE G (8)	☐ REMY V (6)	☐ UHART M (5)	☐ VAN ROSMALEN J (4)
☐ BERKHOF J (7)	☐ SETIAWAN D (6)	☐ WRIGHT TC (5)	☐ ABRAMOWITZ L (3)
☐ BRESSE X (7)	☐ TERMRUNGRUANGLERT W (6)	☐ ZETHRAEUS N (5)	☐ ANONYMOUS (3)
☐ CANFELL K (7)	☐ WESTRA TA (6)	☐ ALJUNID S (4)	☐ AUGUSTOVSKI F (3)
☐ DASBACH EJ (7)	☐ WILSCHUT JC (6)	☐ ANNEMANS L (4)	☐ BAI P (3)
☐ FRANCO EL (7)	☐ ANDERSSON S (5)	☐ BIANIC F (4)	☐ BANSIL P (3)

Triangulation has benefited from multidisciplinary teams of investigators. In the design and implementation of the HPV projects, I had the opportunity to lead and coordinate the research effort of a variety of academic specialisms, aiming to add different perspectives to the definition of the research question and the development of quantitative models representative of the Italian healthcare setting. This approach justifies the number of Authors acknowledged in each published paper submitted. As project leader, my first contribution was to identify, recruit and facilitate the work of leading experts. Although complex, multi-location teams are relatively difficult to manage, it was imperative to acquire the highest number of inputs possible to inform the models. Most of the relevant perspectives have been included in the analysis from leading:

- Epidemiologists;

- Clinicians;

- Public Health executive;

- Payors (Italian NHS);

-Health-economic specialists;

- Bayesian modelers;

- Statisticians.

1.2 Method triangulation

Methodological triangulation involves the use of more than one kind of method to address the same research question. Benefits were found in the confirmation of findings and an increased validity such as the better understanding of the research outcomes. Although many researchers have adopted this technique, few examples have been published [34].

The five published papers submitted for examination provide a unique case for method triangulation. I directly contributed to the methodological choices underpinning all five submitted papers, following a clear trajectory leading from the first static model (Paper 1) to a more comprehensive Bayesian cost-effectiveness analysis (Paper 4) and future developments in the estimate of the social value of gender-neutral HPV vaccination (Paper 5).

Paper 1 represents the starting point. In this work we adopted a basic Markov static model to "estimate the incidences of detected precancerous lesions and cervical cancer". Moreover the model assessed the "cervical cancer mortality rate, lifetime risks of precancerous lesions and cervical cancer, deaths due to cervical cancer, remaining life expectancy and quality-adjusted life years (QALYs)". Using this approach the total direct medical costs related to the cervical cancer screening, the HPV vaccination programme and the management of the HPV-related diseases were calculated. Finally, we divided the incremental costs by the incremental health outcomes (number of life-year gained (LYG) or QALY gained) to obtain the incremental cost-effectiveness ratios (ICERs).

Paper 2 addressed a fundamental methodological issue of cost-effectiveness analysis, the validity of the method used to elicit patient utilities. This economic parameter is instrumental to the correct calculation of the QALY, the denominator in the cost-effectiveness ration (ICER).

This "multicentre, observational, retrospective, cross-sectional pilot study" was part of a larger research project comprising four studies. It was designed to elicit health state preferences (utilities) in a cohort of patients with a histologically confirmed diagnosis of CIN2-3. Among HPV-related diseases (e.g., invasive cervical cancer), it was expected that such lesions would have been perceived with wide variability in affecting the patients' quality of life.

Paper 3 posed the question of the optimal vaccination coverage given budgetary constraints. The access to publicly funded vaccination is indeed another critical input that highly influences the outcomes of cost-effectiveness analysis of HPV immunisation strategies. A bound optimisation model was then used due to the several ex-ante constraints that may affect the allocation of resources among healthcare programmes. This, allows decision makers to maximise the total expected benefits for a given budget.

In paper 4, the methodological learning acquired in the implementation of our previous research was applied to the modelling of gender-neutral vaccination policy in Italy by using a dynamic Bayesian model of the cost-effectiveness. By adopting this dynamic model, we accounted for interactions between individuals of different sex in the definition of the transition probabilities from "Exposure" to "Infection." As such, the HPV transmission was estimated for the first time using the dynamic force of infection, which is defined as a "function of HPV transmission probabilities, partner acquisition rates, and population prevalence". To do so, all parameters were given suitable probability distributions, to reflect the state of science. However, as a common feature of pathogenesis in human medicine, most parameters were subject to a considerable amount of uncertainty that was propagated through the model using Markov chain Monte-Carlo estimation.

The uncertainty observed in paper 4 in the distribution of clinical parameters led to the need for the reassessment of all the randomised clinical trials. This was the aim of the systematic review of the published clinical literature adopted as the main method for Paper 5. A systematic review of the extant literature was conducted on the efficacy, immunogenicity, and safety of the new 9-valent vaccine against HPV (HPV9), as well as a systematic search of the registered, completed, active, and/or ongoing clinical trials (RCTs) on HPV9. The methodological rigour of systematic review of the literature allowed to reduce the heterogeneity of the outcomes, leading to the collection of a robust set of inputs, including efficacy, immunogenicity, and safety outcomes, which will

inform the next generation of cost-effectiveness studies of gender-neutral vaccination strategies aimed to eradicate the HPV threat and to cancel the economic burden of diseases imposed on society by HPV-induced malignancies.

1.3 Data Triangulation

The triangulation of data occurs when multiple theories, materials or methods are used. Data triangulation validates data increases the internal credibility and validity of research outputs.

Although data analysed were referring to one setting (the Italian population and healthcare system), the five papers submitted for examination followed an unprecedented variety of data collection approaches.

In Paper 1, available Italian epidemiological data were used to inform the model. Then, the model was empirically calibrated hierarchically to fit HPV prevalence rate as well as age-specific incidence and mortality rates of cervical cancer, as it was observed among the Italian screened population. However, the underlying natural history of cervical cancer was assumed to be fundamentally the same across countries. In fact, it is well acknowledged that "the patterns of sexual behavior and the age of sexual debut may vary" [35]. To take into account this variation, the incidence rates of HPV infection were adjusted to the Italian epidemiological published evidence.

In paper 2, three clinical research centres, located in north, centre and south of Italy, were involved in the study to provide primary data. The following criteria were used to identify the eligible patients: "age between 18 and 65 years at the time of diagnosis; a histologically confirmed diagnosis of CIN2-3; a recorded surgical procedure of hospital conisation; and time from conisation to administration of questionnaires 78 weeks (to avoid the potential impairment effect of recollection that might be associated with a stressor event)". We excluded patients who did not fully complete the questionnaires used to measure utilities and quality of life and those with an incomplete clinical record.

The secondary data used to inform the bound optimization model developed in Paper 3 were also provided by participating Italian Healthcare trusts. Specifically, five Local Healthcare Authorities in the Basilicata Region were involved and data on rates of screening and vaccination, allocation of budgets and costs (including the total spent on prevention) were retrieved on a real base.

The regional demographic archive provided information on "subjects' date of birth, sex and healthcare identification number, whereas data on the course of vaccination (including the patients' names and healthcare identification numbers, together with dates of issue, brand names and batch numbers of the vaccine) were obtained from the regional vaccination register". All personal data were replaced with a univocal numerical code to ensure that both information was anonymous at the source.

In Paper 4, we considered the proportion of infected individuals in the population available for mating at a given time and under the three alternative interventions. This was made to estimate the HPV population dynamically. The force of infection was then computed as the product of these three terms and resulted in rates that were rescaled into probabilities.

Lastly, the systematic review of the literature reported in Paper 5 was conducted followed the systematic approach named "PRISMA" (Prepared Items for Systematic Reviews and Meta-Analysis) guidelines. In this paper, published studies were retrieved from the electronic databases Medline, Embase and the Cochrane Library. The database search strategies were built around 9vHPV-related free-text keywords. Besides, further studies were identified and downloaded from reference listing of relevant articles and consultation with experts in the field. Registered clinical trials were identified from clinical trials' registries and platforms such as the WHO ICTRP (International Clinical Trials Registry Platform), the ClinicalTrials.gov registry, the Cochrane Central Register of Controlled Trials and the EU Clinical Trial Register.

2. Personal contribution to research output

In addition to my contributions to the development of the overarching research plan, I also directly contributed to the research outputs of each published paper submitted for examination.

My contributions to outputs reflect the expected research skills to be demonstrated upon conferment of a Doctoral Degree:

- Review of the literature (Papers 1, 4, 5)
- Formulation of research question (Papers 1, 2, 3, 4, 5)
- Choice of methods (Papers 1, 2, 3, 5)
- Data collection (Papers 1, 3, 5)

- Data analysis (Papers 2, 3, 5)
- Analysis of limitations of the research (Papers 1, 2, 3, 4, 5)
- Conclusions and recommendations (Papers 1, 2, 3, 4, 5)

My contribution to the outputs of each published paper submitted for examination is summarised below in a schematic form.

1) **Personal contributions Paper 1:**

1. Coordination of the scientific project;
2. Literature review;
3. Research question;
4. Design of the economic model;
5. Data collection of the inputs relevant to inform the model
6. Draft of the conclusions;
7. Analysis of limitations;
8. Contribution to the writing of the paper.

2) **Personal contributions Paper 2:**

1. Coordination of the scientific project;
2. Research question;
3. Design of the economic model;
4. Choice of the questionnaire used to collect data;
5. Preliminary analysis of collected data;
6. Analysis of limitations;
7. Contribution to the writing of the paper.

3) **Personal contributions Paper 3:**

1. Coordination of the scientific project;
2. Research question;
3. Design of the economic model;
4. Data collection and verification with participating local Councils (ASLs);
5. Data analysis;
6. Draft of the conclusions (political economics);
7. Analysis of limitations;
8. Contribution to the writing of the paper.

4) **Personal contributions Paper 4:**

1.   Coordination of the scientific project;
2.   Literature review;
3.   Research question;
4.   Contribution to the design of the cost-effectiveness model;
5.   Draft of the conclusions;
6.   Analysis of limitations;
7.   Contribution to the writing of the paper.

5) **Personal contributions Paper 5:**

Being the only health economist involved in the project, I conducted all stages of research:

1.   Coordination of the scientific project;
2.   Literature review;
3.   Research question;
4.   Data collection from the extant literature of all inputs informing the review;
5.   Data analysis;
6.   Analysis of limitations;
7.   Conclusions;
8.   Contribution to the writing of the paper.

3. Research impact

The BEST II cost-effectiveness study (Paper 4) extended the previously published model Paper 1), including population dynamics in an open model structure, a range of HPV-induced diseases, and the dynamical effects of sexual mixing to account for herd immunity. The study concluded that universal vaccination targeting the 12-year age group is extremely cost effective in comparison to female-only vaccination. The cost per QALY gained was calculated as €11,600, well below the value of €30,000 that is usually considered to be the threshold of good value for money in healthcare policy.

Based on the outcomes of the BESTII study, in January 2017 the Italian Prime Minister Paolo Gentiloni signed a new Levels of Care agreement for the Italian health service that made Italy the first EU country and G8 nation to adopt a nationwide gender-neutral HPV vaccination programme.

The following month, the National Vaccination Plan was published in full by the Italian Minister of Health. This vaccination plan cites the BEST study as evidence of the cost-effectiveness of vaccinating boys.

Abstracts of the published papers submitted for examination

Paper 1

"OBJECTIVE:

This study aimed to determine the health impact and cost-effectiveness of introducing a human papillomavirus (HPV) vaccination programme with a quadrivalent vaccine alongside the existing cervical cancer screening programme in comparison to the current context in Italy.

METHODS:

A US Markov model was adapted to the Italian context, assuming under base case 80% vaccine coverage rate, lifetime duration of protection in a cohort of girls aged 12 years and discount rates of 1.5% and 3% for health benefits and costs, respectively, and estimating direct medical costs.

RESULTS:

The HPV vaccination in association with the current screening programme would allow avoiding 1432 cases of cervical cancer (-63.3%) and 513 deaths (-63.4%) compared to screening only, with an incremental cost-effectiveness ratio (ICER) of 9569 euros per additional quality-adjusted-life-year (QALY) gained. The sensitivity analysis highlighted that this model was robust to all parameters presenting uncertainties as the ICERs ranged from 2,781 euros to 48,122 euros per QALY gained.

CONCLUSION:

This study showed that HPV vaccination in adolescent girls would be a beneficial and cost-effective public health programme in Italy".

Paper 2

"BACKGROUND:

The economic evaluation of any human papillomavirus (HPV) vaccination strategy requires the measurement of clinical benefits (quality-adjusted life-years [QALY]) gained to reflect both the increase in life expectancy and the economic benefits associated with an effective intervention.

OBJECTIVE:

The purpose of this pilot study was to investigate the feasibility of a standardized time trade-off (TTO) procedure to quantify utility loss in health states affected by HPV-induced pathologies in Italy.

METHODS:

This multicenter, retrospective, observational, cross-sectional study was designed to elicit data on utilities in a cohort of women with a histologically confirmed diagnosis of high-grade cervical intraepithelial neoplasias (CIN2-3). An algorithm for the computerized administration of a TTO questionnaire was developed for the standardized elicitation of data on health utilities in CIN2-3, anogenital warts, and invasive cervical cancer. The European Quality of Life-5 Dimensions (EQ-5D) questionnaire was used to assess the respondents' baseline perception of their health conditions. The correlation between utilities and age, time from conization to questionnaire administration, and EQ-5D score, was tested using the Spearman rank correlation coefficient (ρ) as a measure of validity.

RESULTS:

Of 42 enrolled patients, 36 responded (85.7%) (mean [SD] age, 37.2 [9.0] years). The women's perception of their health state was high (mean [SD] EQ-5D score, 0.93 [0.10]). The mean utility values were 0.73 (0.22), 0.71 (0.35), and 0.02 (0.08) for CIN2-3, anogenital warts, and invasive cervical cancer, respectively. Based on ρ values, none of the 3 HPV-induced pathologies considered was significantly correlated with utility. Nonsignificant variability was found among utilities elicited for anogenital warts (range, 0.54 [0.47] to 0.79 [0.27]); this variability was a limitation of this pilot study and was likely the result of the limited sample size.

CONCLUSIONS:

Based on the findings from this pilot study, a TTO standardized procedure is expected to be feasible and appropriate for assessing utilities in patients affected by HPV-related diseases and for cost-effectiveness analyses of cervical cancer prevention in Italy".

"OBJECTIVES:

The GIOVE Study was aimed at the achievement of the allocative efficiency of the budget allocated to the prevention of human papillomavirus (HPV)-induced diseases. An ex-ante determination of the most efficient allocation of resources between screening and multicohort quadrivalent immunisation programmes was followed by the ex-post assessment of the allocative efficiency achieved after a 12-month period.

DESIGN:

A bound optimisation model was developed to determine the ex-ante allocative efficiency of resources. The alternatives compared were the screening programme alone and the quadrivalent immunisation with access to screening. A sensitivity analysis was carried out to assess the uncertainty associated with the main inputs of the model. Subsequently, a cohort of girls with a complete recorded vaccination history was enrolled in an observational retrospective study for 18 months to ensure full compliance with the recommended schedule of vaccination (0, 2, six months) within a 12-month time horizon.

SETTING:

Basilicata region, in the south of Italy.

PARTICIPANTS:

12 848 girls aged 12, 15, 18 or 25 years.

INTERVENTION:

Immunisation with quadrivalent anti-HPV vaccine.

OUTCOME MEASURES:

The vaccination coverage rate was considered to be the indicator of the best possible benefit, given the budgetary constraints.

RESULTS:

Assuming a vaccine price of €100 per dose, a vaccination coverage rate of 59.6% was required for the most effective allocation of resources. The optimal rate of coverage was initially in favor of the multicohort strategy of vaccination against HPV (72.8%±2%). When the price paid for the quadrivalent vaccine dropped to €85 per dose, the most efficient coverage rate (69.5%) shifted closer to the immunisation rate achieved during the 12-month observation period.

CONCLUSIONS:

The bound optimisation model demonstrated to be a useful approach to the ex-ante allocation and the ex-post assessment of the economic resources allocated to a multicohort quadrivalent anti-HPV vaccination programme".

Paper 4

"BACKGROUND:

Human papillomavirus (HPV) is the main causative agent of benign and malign neoplasms in both sexes. The Italian recommendations for HPV vaccines consider only females. The BEST II study (Bayesian modelling to assess the Effectiveness of a vaccination Strategy to prevent HPV-related diseases) evaluates 1) the cost-effectiveness of immunization strategies targeting universal vaccination compared with cervical cancer screening and female-only vaccination and 2) the economic impact of immunization on various HPV-induced diseases.

OBJECTIVE:

The study aimed to evaluate whether selective or universal vaccination was the most cost-effective intervention against HPV.

METHODS:

We present a dynamic Bayesian Markov model to investigate transmission dynamics in cohorts of females and males within a 55-year timeframe. We assumed that quadrivalent vaccination (against HPV 16, 18, 6, and 11) is available for 12-year-old individuals. The model simulates the progression of infected subjects across HPV-induced health states (cervical, vaginal, vulvar, anal, penile, and head/neck cancer and anogenital warts). The sexual mixing is modeled by age-, sex-, and sexual behavioral-specific matrices to obtain the dynamic force of infection.

RESULTS:

In comparison to cervical cancer screening, universal vaccination results in an incremental cost-effectiveness ratio of €1,500. When universal immunization is compared with female-only vaccination, it is cost-effective with an incremental cost-effectiveness ratio of €11,600. Probabilistic sensitivity analysis shows a relatively large amount of parameter uncertainty, which interestingly has, however, no substantial impact on the decision-making process. The intervention being assessed seems to be associated with an attractive cost-effectiveness profile.

CONCLUSIONS:

Universal HPV vaccination is a cost-effective strategy when compared with either cervical cancer screening or female-only vaccination within the Italian context".

Paper 5

Abstract:

"In 2014, the Food and Drug Administration approved a new human papillomavirus 9-valent vaccine (9vHPV), targeting nine HPV types: HPV types 6, 11, 16, and 18, which are also targeted by the quadrivalent HPV vaccine (4vHPV), plus five additional high cancer risk HPV types (HPV types 31, 33, 45, 52, and 58). The current study aimed to retrieve systematically, qualitatively and quantitatively pool, as well as critically appraise all available evidence on 9vHPV from randomized controlled trials (RCTs). We conducted a systematic review of the literature on 9vHPV efficacy, immunogenicity and safety, as well as a systematic search of registered, completed, and ongoing RCTs. We retrieved and screened 227 records for eligibility. A total of 10 publications reported on RCTs' results on 9vHPV and were included in the review. Sixteen RCTs on 9vHPV have been registered on RCT registries. There is evidence that 9vHPV generated a response to HPV types 6, 11, 16 and 18 that was non-inferior to 4vHPV vaccine. Vaccine efficacy against five additional HPV type-related diseases was directly assessed on females aged 16-26 years (risk reduction against high-grade cervical, vulvar or vaginal disease = 96·7%, 95% CI 80·9%-99·8%). Bridging efficacy was demonstrated for males and females aged 9-15 years and males aged 16-26 years (the lower bound of the 95% CIs of both the geometric mean titer ratio and the difference in seroconversion rates meeting the criteria for non-inferiority for all HPV types). Overall, 9vHPV has been proved to be safe and well tolerated. Other RCTs addressed: 9vHPV co-administration with other vaccines, 9vHPV administration in subjects that previously received 4vHPV and 9vHPV efficacy in regimens containing fewer than three doses. The inclusion of additional HPV types in 9vHPV offers great potential to expand protection against HPV infection. However, the impact of 9vHPV on reducing the global burden of HPV-related disease will greatly depend on vaccine uptake, coverage, availability, and affordability".

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