

Institution: University College London		
Unit of Assessment: 10 – Mathematical Sciences		
Title of case study: Novel methods for cost-effectiveness analysis, decision making problems and disease prevention		
Period when the underpinning research was undertaken: 2005-2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Gianluca Baio	Professor of Statistics and Health Economics	2005 - present
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact (indicative maximum 100 words)		
<p>Researchers in the UCL Department of Statistical Science (DSS) contributed to changes to policies and guidelines for HPV vaccination in Italy, the UK and Canada. Their work demonstrated the potential for cost-effectiveness of a universal vaccination strategy (in comparison to simple screening programmes or targeted vaccinations for young females only). As a result, the annual overall expenditure for HPV vaccines in Italy increased by 17.4% in 2017, generating an estimated income to the manufacturers of approximately EUR22,500,000 (approximately GBP19,800,000). UCL DSS research has also informed the national Meningococcal group B bacteria vaccination programme in the UK that led to a 62% decrease in meningococcal disease cases over the first three years of the programme.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>Professor Baio's research focuses on developing Bayesian modelling for cost-effectiveness analysis and decision-making problems in health systems. This type of model is used to support the submission of new health care interventions (typically medicines) to regulatory agencies – such as the National Institute for Health and Care Excellence (NICE) in England – which, in turn advise governments on whether public funds should be used to pay for these interventions.</p> <p>Typically, the effectiveness of vaccination strategies is evaluated using dynamic compartmental models fitted solving Ordinary Differential Equation systems (ODEs) in continuous time. While accounting for infection dynamics (representing the “industry standard”), they are computationally burdensome, particularly in realistic situations characterised by a large number of “states”. More importantly, it is hard to propagate in a principled way the joint uncertainty of all the model parameters. This is paramount in medical decision making, and amounts to a procedure in which all input parameters are considered as random quantities and are therefore associated with a probability distribution that describes the state of science (<i>ie</i> the background knowledge of the decision maker). This is typically referred to as “probabilistic sensitivity analysis” (PSA) [R1].</p> <p>To overcome the crucial limitation of ODE based models in the application of PSA, Professor Baio and his research group developed a modelling framework based on a Bayesian evidence synthesis of the most relevant sources, coupled with a computationally efficient version of a Markov model (MM) – a version of multistate models widely used in Health Technology Assessment (HTA). Specifically, the research team developed a Bayesian dynamic Markov model [R2, R3], to allow for herd immunity and dynamic transmission of infection. This is based on discrete time cycles and the model uses a lower temporal resolution in comparison with standard ODEs. It also allows one to obtain</p>		

calibrated estimates of the underlying population dynamics (in terms of progression to infection and re-infections, in addition to other relevant health states) at a fraction of the computational time. Consequently, Professor Baio's research team were able to consider a complex structure (over 50 interconnected health states) and to fully propagate the joint uncertainty, where limited empirical evidence was present, into the model parameters.

This novel approach has been applied to the BESTII study [R4] to assess:

1. the cost-effectiveness of a new vaccination strategy aimed at reducing the burden of Human Papilloma Virus (HPV), one of the leading causes of cancer of female and male genital system, anus, oropharyngeal, anogenital warts, and recurrent respiratory papillomatosis.
2. the benefits and costs of expanding coverage to both females and males – specifically in 12-18 year olds.

Professor Baio's team led on all the methodological and modelling aspects of the research, including the design and conduct of the analysis. As a result, and in line with standard HTA requirements (that inform regulatory guidance, eg NICE), their model was able to:

- demonstrate the potential for cost-effectiveness of a universal vaccination strategy (in comparison to simple screening programmes or targeted vaccinations for young females only);
- provide a full characterisation of the level of uncertainty around the suggested decision-making process.

The research underpinning this case study has been conducted by the "Statistics for Health Economic Evaluation" research group, led by Gianluca Baio (Reader 2014-2018; Professor of Statistics and Health Economics 2018-) and including Katrin Haeussler (PhD student 2011-2015), Anna Heath (PhD student 2014-2018; now at University of Toronto, Canada, as Assistant Professor), Andrea Gabrio (PhD student 2014-2018; now at Erasmus University, Netherlands, as Assistant Professor), Ioanna Manolopoulou (Lecturer 2014-2018), Ardo van den Hout (Lecturer, 2011-2015) and other collaborators.

3. References to the research (indicative maximum of six references)

[R1] Baio G, Dawid AP. (2015). Probabilistic sensitivity analysis in health economics. *Stat Methods Med Res.* Dec;24(6):615-34. doi:10.1177/0962280211419832.

[R2] Haeussler, K, Marcellusi, A, Mennini, FS, Favato, G, Picardo, M, Garganese, G, Bononi, M, Costa, S, Scambia, G, Zweifel, P, Capone, A, Baio, G. (2015). Cost-effectiveness analysis of universal human papillomavirus vaccination using a dynamic Bayesian methodology: The BEST II study. *Value in Health.* 18(8)956-968 doi:10.1016/j.jval.2015.08.010

[R3] Haeussler, K, van den Hout, A, Baio G. (2018). A dynamic Bayesian Markov model for health economic evaluations of interventions against infectious diseases. *BMC Medical Research Methodology*, 18(82). doi:10.1186/s12874-018-0541-7

[R4] Mennini, FS; Bonanni, P; Bianic, F; De Waure, C; Baio, G; Piazzotta, G; Uhart, M; Rinaldi, A; and LARGERON N. (2017). Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. *BMC Cost Effectiveness and Resource Allocation*, 15(11). doi:10.1186/s12962-017-0073-8

4. Details of the impact (indicative maximum 750 words)

Professor Baio's BESTII research on the decisions to fund the nine-valent HPV vaccine have been cited directly by several international jurisdictions in Italy, Canada and the UK, with authorities later modifying policy guidance for HPV vaccination based on Professor Baio's recommendation. The policy change has led to the extension of HPV vaccination programme to 2,000,000 males in Italy (with approximately 35% already vaccinated), generating savings of approximately EUR71,000,000 per year for the Italian national healthcare service. In addition, Professor Baio's research on the cost-effectiveness of

Meningococcal group B bacteria vaccination informed policy changes and promoted the protection of 800,000 babies per year in the UK.

Extending the vaccination programme against HPV in Italy

Italian teams of economists collaborating with the UCL research team presented the BESTII study results to the Italian Medicines Agency and Servizio Sanitario Nazionale (SSN; the Italian equivalent of NHS). The latter used these results as part of the evidence base to motivate changes in the national guidelines on the vaccination programmes ('Piano Nazionale Prevenzione Vaccinale', PNPV 2017-2019), which were revised in January 2017 to expand HPV vaccination to 12-18 year old males. **The PNPV 2017-2019 guideline directly cites the UCL team's work as evidence** to EUR71,000,000 reduction of direct costs estimated for diseases caused by HPV virus: "a recent economical evaluation model (...) estimates a 64% reduction of HPV-related events in males following a universal vaccination" (**S1**). Following this change in regulation, the SSN covered the costs of HPV vaccinations for approximately 2,000,000 males aged 12 to 18 years old (**S2**). The long-term savings for SSN are estimated at EUR71,000,000 per year (approximately GBP63,000,000) (**S1**), due to a reduction in male HPV-related diseases and their subsequent diagnosis and treatment.

Economic impact on the HPV vaccine manufacturers

The development of more advanced quadrivalent vaccination exhibited a potential benefit through targeting 4 strains of HPV. However, it involved higher acquisition costs compared to the bivalent vaccine, which at the time was provided in Italy for female vaccination at the age of 12-15 years old, in accordance with national guidelines. In addition, there was inconsistent evidence regarding the potential effects on population health of including young males in the vaccination programme. As a result of the impact of the BESTII study [**R2**] and the subsequent change in the Italian guidelines, the overall annual expenditure for HPV vaccines in Italy increased by 17.4% in 2017. The Italian National Vaccination Plan provides universal anti-HPV vaccination with Gardasil-9 produced by Merck, with **an estimated income for the vaccine manufacturer of EUR23,100,000 (S3)**.

Informing policy changes to the HPV vaccination programme in the UK

Results from underpinning research informed the letter that Professor Giampiero Favato wrote to the then UK Health Secretary Jeremy Hunt on 13th June 2016, urging the UK Government to extend the national HPV vaccination programme to include all adolescent boys, potentially protecting over 400,000 boys per year (**S4**). In addition, these results were part of the evidence presented to the Joint Committee on Vaccination and Immunisation (JCVI), the UK's independent expert advisory committee to ministers and health departments on immunisation. In July 2018, the JCVI concluded that "(...) a gender neutral programme would provide resilience against short-term fluctuations in uptake as well as offer the prospect of better control of the main cancer causing types of HPV" (**S5**), thus resulting in **the Government's implementation of the gender-neutral HPV vaccination in the UK since September 2019**. Currently, 12 and 13 year olds are routinely offered the first HPV vaccination, while a second dose is offered 6 to 24 months later (**S5**).

Officials stated that **the universal vaccination programme is "[...] firmly grounded in evidence** to ensure that we can get the best outcomes for patients", while the Head of Immunisations at Public Health England stated: "I'm pleased that adolescent boys will be offered the HPV vaccine. Almost all women under 25 have had the HPV vaccine and we're confident that we will see a similarly high uptake in boys. This extended programme offers us the opportunity to make HPV-related diseases a thing of the past and build on the success of the girls' programme, which has already reduced the prevalence of HPV 16 and 18, the main cancer-causing types, by over 80%. We can now be even more confident that we will reduce cervical and other cancers in both men and women in the future" (**S6**).

Towards establishing a universal vaccination programme against HPV in Europe and Canada

The BESTII study, together with other evidence, **informed the European Parliament's European Immunisation Week campaign in 2017**, which saw the launch of a new report: "Improving health equity and cancer prevention outcomes: HPV vaccination for boys and girls" (**S7**). Moreover, the BESTII study has also provided evidence on the cost-effectiveness of adding males to current HPV vaccination protocols to "Public consultation on draft guidance for introduction of HPV vaccines in EU countries: focus on 9-valent HPV vaccine and vaccination of boys and people living with HIV" from the European Centre for Disease Prevention and Control in April 2019 (**S7**). Indeed, many more countries have already implemented or are preparing to implement universal HPV vaccination, including Croatia, Norway, Germany, Serbia, and New Zealand (**S7**). The results from the BESTII study were also part of the evidence on the economic advantages of extending HPV vaccination age in both females and males that **informed the Canadian guidelines on HPV immunization programme**. Based on BESTII and other reviewed studies, The Canadian Agency for Drugs and Technologies in Health extended the vaccination programme to males up to 26 years old (**S7**).

Informing policy changes to the Meningococcal group B bacteria vaccination programme in the UK

In 2013, the JCVI decided against recommending the use of Bexsero, the first vaccine developed against Meningitis B bacteria (MenB; one of the leading infectious killers in young children, with 5% mortality rate, and responsible for more than 90% of meningococcal infections in children under one). Bexsero had been approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) and was one of only two vaccines available against MenB. The decision was based on the analysis, developed by researchers at Warwick and the London School of Hygiene & Tropical Medicine (LSHTM), of the impact and cost-effectiveness of different vaccination strategies using a model based on ODE's, which concluded that the vaccine did not represent value-for-money, at the price requested by the manufacturer (originally Novartis).

[TEXT REDACTED FOR PUBLICATION]

Bexsero (then marketed by GSK) was added to the UK infant immunization schedule starting from September 2015, enabling the annual protection of 800,000 babies (at a cost of GBP16,000,000). In the first three years of the vaccination programme against MenB, cases of **the disease decreased by almost 62% in children who received at least two doses**. Specifically, between 2015 and 2018, an estimated 277 out of 446 expected cases were prevented because of the vaccine (**S10**).

5. Sources to corroborate the impact (indicative maximum of 10 references)

- S1. SSN guidelines on the vaccination programmes (PNPV 2017-2019, page 86) corroborate figures on reduction of HPV-related diseases in males and costs of their treatment.
- S2. Italian National Statistics Institute corroborates number of males included in vaccination programme.
- S3. AIFA 2017 National report on the usage of medicines in Italy corroborates the information and figures for annual expenditure and recommendation for 9-valent HPV vaccine.
- S4. Transcripts of the letter sent to the Health Secretary Jeremy Hunt to the Secretary of State (13/06/2016) in the UK corroborate the request of extension of the national HPV vaccination programme supported by the underpinning research.
- S5. HPV Vaccination from 2018 and NHS public health functions agreement 2019-20 (Service specification No.11) published in July 2019 corroborate recommendation of HPV vaccine for males 12-18 years old.
- S6. News story published on the UK Government website (24/07/2018) corroborates statement from the Head of Immunisations at Public Health England UK on benefits of HPV vaccination in the UK.

Impact case study (REF3)

S7. Canadian Agency for Drugs and Technologies in Health report published on 24th March 2017 (page 7-9); European Centre for Disease Prevention and Control guidelines (01/04/2019; page 12, 52,64,70); Articles published in Vaccines Today (25/04/2017) and Health Europa (23/04/2018) - corroborate that [R2] was used as an evidence to inform guidelines and reports.

[TEXT REDACTED FOR PUBLICATION]

S10. Public Health of England study published in New England Journal of Medicine journal corroborates the decrease of meningitis cases in children included in vaccination programme against MenB between 2015 and 2018.