Taylor & Francis
Taylor & Francis Group

Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierv20

Public health impact and return on investment of the pediatric National Immunization Program in Italy

Marco Barbieri, Sandra E. Talbird, Justin Carrico, Sara Boccalini, Angela Bechini, Paolo Bonanni, Claire E. Mellott, Francesca Senese, John Cameron Lang & Goran Bencina

To cite this article: Marco Barbieri, Sandra E. Talbird, Justin Carrico, Sara Boccalini, Angela Bechini, Paolo Bonanni, Claire E. Mellott, Francesca Senese, John Cameron Lang & Goran Bencina (2024) Public health impact and return on investment of the pediatric National Immunization Program in Italy, Expert Review of Vaccines, 23:1, 974-985, DOI: 10.1080/14760584.2024.2411425

To link to this article: https://doi.org/10.1080/14760584.2024.2411425

EXPERT REVIEW OF VACCINES
2024, VOL. 23, NO. 1, 974–985
https://doi.org/10.1080/14760584.2024.2411425

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Public health impact and return on investment of the pediatric National Immunization Program in Italy

Marco Barbieri[a], Sandra E. Talbird[b], Justin Carrico[b], Sara Boccalini[c], Angela Bechini[c], Paolo Bonanni[c], Claire E. Mellott[b], Francesca Senese[d], John Cameron Lang[e] and Goran Bencina[f]

[a]York Health Economics Consortium, University of York, York, UK; [b]RTI Health Solutions, Research Triangle Park, NC, USA; [c]Department of Health Sciences (DSS), University of Florence, Florence, Italy; [d]MSD Italy, Rome, Italy; [e]Biostatistics and Research Decision Sciences, Merck Canada Inc., Quebec, Canada; [f]Outcomes Research, Value & Implementation, MSD, Madrid, Spain

ABSTRACT

Objectives: We conducted a cost–benefit analysis of the pediatric National Immunization Program (NIP) in Italy.

Methods: An economic model evaluated the benefit–cost ratio (BCR) of the Italian pediatric NIP, including 10 pathogens for mandatory vaccines and 4 pathogens for recommended vaccines for children aged 0–10 years from the healthcare-sector and societal perspectives. Separate decision trees were used to model each vaccine-preventable disease (VPD). The 2020 birth cohort ($n = 420,084$) was followed over their lifetime; the model projected and compared discounted disease cases, life-years, quality-adjusted life-years (QALYs), and costs (2021 euros) with and without immunization (based on current and pre – vaccine era disease incidence estimates, respectively).

Results: The pediatric NIP was estimated to prevent 1.8 million cases of VPDs and 3,330 deaths, resulting in 45,900 fewer life-years lost and 57,000 fewer QALYs lost. Vaccination costs of €285 million were offset by disease cost savings of €1.6 billion, resulting in a BCR of 5.6 from a societal perspective (BCR = 1.7 from a healthcare-sector perspective). When QALYs gained were valued, the BCR increased to 15.6.

Conclusions: The benefits of the Italian pediatric NIP, including averted disease-related morbidity, mortality, and associated costs, highlight the value of continued investment in pediatric immunization.

ARTICLE HISTORY
Received 19 August 2024
Accepted 27 September 2024

KEYWORDS
vaccination; cost-benefit analysis; mathematical model; children; economic analysis; prevention; infectious disease; benefit–cost ratio

1. Introduction

Vaccines are among the most cost-effective strategies to promote public health, preventing infectious diseases and the associated morbidity, mortality, and disability [1]. It has been acknowledged and recommended that to capture the true value of vaccines and vaccination programs, economic evaluations need to consider both the protection provided to vaccinated individuals and the protection provided to unvaccinated individuals through reduced circulation of pathogens resulting in herd immunity [2]. The ISPOR Task Force for Economic Evaluation of Vaccines further notes that economic evaluations should capture the effect of both direct and indirect effects of vaccination, including benefits and harms, such as serotype replacement and shift in age of risk of infection [3]. Beyond the economic impacts on individuals and the healthcare system, public vaccination programs also have economic implications for society at large [4]. A recent review paper noted that vaccination yields benefits beyond individual protection against an initial vaccine-preventable disease (VPD), including reductions in long-term disease complications, health or productivity gains for caregivers, and benefits at the societal level (e.g. reduced antibiotic use and subsequent antimicrobial resistance, reduced threat of infectious diseases or outbreaks, and enhanced population productivity leading to higher gross domestic product). Because such benefits may not be fully reflected in the economic evidence, the true economic impact of vaccination programs may be underrecognized [5]. Analyzing the return on investment from a societal perspective can improve understanding of the broad economic impact of vaccine programs [6].

Italy has introduced pediatric immunization gradually, establishing a comprehensive pediatric national immunization program (NIP) since 1978 [7,8]. Up to 2016, vaccination against four pathogens (polio, tetanus, diphtheria, and hepatitis B) was mandatory by law for all newborns; all other available vaccines (measles-mumps-rubella, pertussis, *Haemophilus influenzae* type b [Hib], *Streptococcus pneumoniae* [*S. pneumoniae*], and meningococcal C [MenC]) were only recommended (not mandated) in the NIP [9]. The subsequent 2017–2019 NIP encompassed 10 vaccinations (the 6 pathogens included in the hexavalent vaccine [diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and Hib] plus the measles, mumps, rubella, and varicella pathogens included in the measles, mumps, rubella, and varicella [MMRV] vaccine) that

CONTACT Francesca Senese francesca.senese@msd.com MSD Italy, Via Vitorchiano, 151, Rome 00189, Italy

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14760584.2024.2411425

were made mandatory since mid-2017 by a national law for school attendance of children and adolescents aged 0–16 years [10]. The 2017–2019 NIP release and the approval of Law 119/2017 [10] enacting the extension of mandatory vaccinations and the introduction of sanctions against 'anti-vaxxer' physicians were characterized by strong political commitment and by a heated political and media debate [11–13]. The 2017–2019 NIP has newly recommended some vaccines after a period when they were offered only in some regions: rotavirus (RV), varicella, and meningococcal B (MenB), and has maintained the offer of the already recommended Men C vaccine to all children. In addition, Italian regions were allowed to decide autonomously whether to offer the monovalent C or the quadrivalent ACWY (MenACWY) formulation [14]; since the 2017–2019 NIP and continuing with the 2023–2025 NIP, Italy has had one of the most comprehensive pediatric immunization schedules across Europe [8,15,16].

Prior analyses have evaluated the costs, economic impact, and financial rate of return of routine pediatric immunization in Europe and other countries. The cost of vaccination throughout a lifetime in 23 European countries was found to range from €592 (in Romania) to €3,504 per person (in Germany) (year 2022 euros) [17]. In Belgium, for the 2018 birth cohort, pediatric immunization was associated with overall discounted savings of €35 million and €268 million from the healthcare-sector and societal perspectives, respectively, with benefit-cost ratios (BCRs) of 1.4 and 3.2, respectively [18]; similar analyses in Poland estimated even higher BCRs for pediatric immunization (BCRs of 2.2 and 7.6, respectively) [19]. Analyses in the United States (US) have also consistently shown a positive return on investment for the childhood vaccination program, even as it has expanded over the last 20 years to include additional vaccines [20–22].

Prior economic evaluations have been conducted in Italy to evaluate the inclusion of new pediatric vaccines in the NIP, such as the hepatitis B vaccine, MenB vaccine, pneumococcal conjugate vaccine (PCV), RV vaccine, varicella vaccine, and influenza vaccine [23–30]. These studies are valuable to understand the incremental costs, health gains, and cost-effectiveness of introducing a new vaccine into the Italian NIP; however, due to constraints on immunization budgets, it is also valuable to evaluate the overall economic impact of the pediatric immunization program. To our knowledge, this is the first study to evaluate the public health benefits and economic impact of the 2017–2019 Italian pediatric NIP using actual vaccination coverage rates (VCRs).

The objective of this analysis was to estimate the public health impact and return on investment of the Italian pediatric NIP for children ages 10 years and younger.

2. Methods

2.1. Model description

We developed a decision tree model in Microsoft Excel (Microsoft, Redmond, WA) to estimate the health and economic impact of the Italian NIP. The model focused on the following vaccines included in the Italian NIP for children less than 10 years of age: hexavalent (diphtheria, tetanus, acellular pertussis, and inactivated poliovirus [DTaP-IPV]-hepatitis B [HepB]-Hib), MMRV, MenB, MenACWY, PCV, and RV. Influenza vaccination, while recently recommended for children aged 6 months to 6 years [31], was excluded from the analysis due to the recency of the recommendation in children and low current uptake [32]. The 2020 Italian birth cohort was modeled and followed for their lifetime according to age-specific life expectancy in Italy in 2020 [33]. Vaccination of the birth cohort was modeled using historic VCRs [34,35] and timing of vaccination doses according to Italy's recommended immunization schedule for children during the first 10 years of life [36]. Separate decision trees were used to calculate the health outcomes and costs of each VPD covered by the NIP.

The model structure, which was used to analyze the routine childhood immunization program in the US, has previously been described [20]. Briefly, two analytical scenarios were constructed: one in which routine pediatric immunization occurred according to the Italian NIP, and one in which no immunization occurred.

- For the 'With NIP' analysis, incidence rates per 100,000 for each of the modeled diseases were calculated on the basis of incidence from either 2018 (where available) or the most recent year available.
- For the 'No NIP' analysis, incidence rates were taken from published sources reflecting pre-vaccine incidence from the year prior to routine recommendation of each specific vaccine.

The model calculated and compared health outcomes (in monetary terms) and costs discounted at 3% per year [37] over the birth cohort's lifetime for the With NIP and No NIP analyses. Outcomes for each analysis were calculated and the following incremental outcomes reported: cases avoided, disease-related deaths averted, life-years (LYs) gained, quality-adjusted LYs (QALYs) gained, disease-related costs averted, and vaccination program costs. Analyses were conducted from both the healthcare-sector perspective and societal perspective.

2.2. Vaccination program costs

We calculated the costs of the NIP for children aged 0–10 years from time zero (birth), with the timing of vaccine costs over the cohort's first 10 years of life based on the immunization schedule (Table 1). For each vaccine, we calculated the number of vaccine doses by multiplying the number of individuals alive in the birth cohort at each recommended age of vaccination by the vaccine coverage rate at that dose. VCRs were based on historical data from 2019 [34], except for RV and MenACWY, which had higher VCRs in 2020 due to the recency of their recommendations [35]. Coverage rates were not adjusted to account for the possibility of a proportion of the birth cohort receiving the vaccine later than the recommended age, as this was out of scope of the analysis.

Cost of the pediatric NIP from the Italian National Health Service (NHS) perspective included vaccine acquisition costs without value added tax (10%) using 2020 prices reported in

Table 1. Italian NIP schedule, vaccine coverage rates, and vaccine acquisition costs.

Vaccine	Age at vaccination	Vaccine coverage rates [34,35][a]
Diphtheria, tetanus, acellular pertussis, and inactivated poliovirus (DTaP-IPV) booster	6 years	88.6%
Hexavalent (DTaP-IPV-HepB-Hib)	3 months, 5 months, 11 months	95.0%
Measles, mumps, rubella, and varicella (MMRV)	13 months, 5 years	94.5%
Meningococcal B (MenB)	3 months, 4 months, 5 months, 13 months	69.0%
Meningococcal ACWY (MenACWY)	13 months	51.3%
Pneumococcal conjugate (PCV)	3 months, 5 months, 11 months	92%
Rotavirus (RV)[a]		62.8% overall
	2-dose series: 3 months, 5 months	34.5%
	3-dose series: 3 months, 5 months, 6 months	28.3%

HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; NIP = National Immunization Program; VCR = vaccine coverage rate.
[a]Rotavirus VCR of 62.8% [34] is split between the 2-dose and 3-dose series as shown in the table, based on estimated market share that 55% of those vaccinated with an RV vaccine receive the 2-dose series and 45% receive the 3-dose series.

the National Report on Medicines use in Italy by the Italian Medicines Agency (Agenzia Italiana del Farmaco; AIFA), which reflected the average prices paid by regions after mandatory rebates for public procured vaccines [38]; an administration cost of €6.80 per vaccine dose administered [39]; vaccine wastage at a rate of 5% to account for unused multi-dose vials [22]; and vaccine-related adverse event costs. Vaccine acquisition and administration costs were calculated by multiplying the number of vaccine doses by acquisition costs per dose and the administration cost per dose and summing costs across all vaccines and discounting to account for the timing of vaccination. Vaccine-related adverse event costs were similarly calculated by multiplying the number of vaccine doses of each vaccine by the respective adverse event rate per 100,000 vaccine doses for that vaccine [40] and by the cost per adverse event [28,41–43]. Adverse event rates and costs per adverse event are summarized in the Supplement (Tables S2-S3).

For the societal perspective, the cost of the pediatric NIP included all direct medical costs described above plus productivity loss costs for caregiver time for vaccination. Because multiple vaccines can be given at a single physician visit, vaccines that are scheduled for the same age (e.g. hexavalent, MenB, PCV, and RV vaccines at 3 months of age) were assumed to be given at the same visit and only incur the cost of time loss for one visit. Thus, productivity loss costs for vaccination were calculated by multiplying the total number of expected visits associated with the NIP schedule by the mean hourly wage of a caregiver. An average wage of €90 - per day (€11.25 per hour) was applied for a caregiver or one parent missing time from work [44]; this was multiplied by 1.2 hours per vaccination visit (taken from a cost-effectiveness analysis of varicella vaccination in Italy [27]) to calculate productivity loss costs. Travel costs for caregivers were assumed to be negligible and excluded from the analysis.

2.3. Disease incidence and health outcomes

We considered incidence data before and after each vaccine was routinely recommended in the Italian NIP (Table 2). Dates for when routine vaccination was introduced in Italy and sources for the incidence data are detailed in Supplement Table S1. Pre-vaccine incidence data for the No NIP analysis were obtained from the published literature; vaccine-era incidence data for the With NIP analysis were based on rates of notifications, preferentially from the National Institute of Health (Epicentro website) or, in absence of primary surveillance systems data, from the Surveillance Atlas of Infectious Diseases (European Centre for Disease Prevention and Control [ECDC]) for Italy in 2018 [45,46]. For both time periods, age-specific incidence was used when available.

Incidence rates were multiplied by disease-specific underestimation factors for VPDs where incidence estimates were unlikely to capture the full burden of disease for various reasons (e.g. underreporting to surveillance system, underdiagnosis, not seeking medical care) (Table 2). Underestimation factors were differentiated between under ascertainment, where underestimated cases are assumed to be uncomplicated or nonmedically attended, and underreporting, where underestimated cases were assumed to be medically attended but not reported to a surveillance system [79]. Underestimation factors were obtained from the published literature or were informed by clinical expert opinion.

Using these adjusted annual pre-vaccine and vaccine-era incidence rates and the most recent all-cause mortality in Italy, the number of cases of disease was calculated for the 2020 birth cohort over the cohort's lifetime on the basis of the number of people alive and at-risk for disease each year. Case-fatality ratios were multiplied by the number of disease cases each year to calculate disease-related deaths.

Life-years lost was calculated overall and for each VPD as the number of disease-related deaths each year multiplied by the discounted life expectancy at the age of premature death based on an Italian life table [33]. QALYs lost due to disease-related death was calculated similarly for each VPD and aggregated across diseases on the basis of the quality-adjusted life expectancy (QALE) at the age of premature death, where discounted QALE was based on age-specific utility weights for the general Italian population [80]. All clinical outcomes were discounted to the present day using an annual discount rate of 3% [37]; both undiscounted and discounted clinical outcomes are presented.

2.4. Quality-of-life impacts

In the model, age-specific utility weights for the Italian population were applied to healthy individuals who were vaccinated and thus protected from infection with a VPD, as well as to individuals who survive infection with one of the modeled VPDs and do not develop a long-term complication (i.e. return to good health) [80]. QALY losses were then calculated

Table 2. Pre-vaccine and vaccine-era disease incidence per 100,000.

	No NIP (pre-vaccine)		With NIP (vaccine era)		
Disease, age group	Incidence per 100,000[a]	Underestimation factor[b]	Incidence per 100,000[a]	Underestimation factor[b]	References
Diphtheria		UR: 1.0		UR: 1.0	[45,47]
<1 y	318.4		0.0		
1-14 y	37.7-82.4		0.0		
≥15 y	1.3-7.0		0.0		
H. influenzae type b		UR: 1.1		UR: 1.0	[48–50]
<5 y	9.0		0.0 - 0.3		
≥5 y	0.0		0.0 - 0.1		
Hepatitis B		UA: 6.0		UA: 6.0	[51,52]
<15 y	6.0		0.0		
15-24 y	42.0		0.0		
≥25 y	7.0		0.0 - 0.7		
IMD (serogroups A, B, C, W, Y)		UR: 3.3		UR: 1.0	[46,49,53]
<1 y	2.4		2.4		
1-24 y	0.4 - 1.1		0.4 - 0.7		
≥25 y	0.0 - 0.1		0.2		
Measles		UR: 10.0		UR: 1.7	[46,54,55]
<5 y	174.3 - 390.7		17.4 - 39.5		
5-29 y	43.8 - 249.7		3.3 - 13.7		
≥30 y	40.2 - 96.7		2.2		
Mumps		UR: 10.0		UR: 1.4	[46,55,56]
<5 y	41.5 - 656.2		1.7 - 17.7		
5-29 y	19.7 - 218.1		0.6 - 8.0		
≥30 y	1.1 - 2.9		0.3		
Pertussis					[45,46,57,58]
<1 y	519.5	UA: 1.8	50.4	UA: 1.8	
1-14 y	105.8 - 308.1	UA: 9.2 - 12.9	5.6 - 9.3	UA: 9.2 - 12.9	
≥15 y	1.3 - 6.9	UA: 12.9	0.1 - 0.8	UA: 12.9	
Polio		UR: 1.0		UR: 1.0	[45]
<5 y	59.0		0.0		
5-14 y	6.0		0.0		
≥15 y	0.8		0.0		
Rotavirus (<5 y only)					[26,59,60]
Hospitalizations	363.8 - 526.0	UR: 1.0	203.0 - 203.3	UR: 1.0	
ED visits	1,481.5 - 3,574.0	UR: 1.0	329.3 - 679.1	UR: 1.0	
Outpatient visits	1,777.7 - 4,289.0	UR: 1.0	471.0 - 1,008.0	UR: 1.0	
NMA cases	11,641.6 -16,832.0	N/A	3,084.4 - 3,955.9	N/A	
Rubella		UR: 10.0		UR: 1.4	[55,61,62]
<5 y	1.4 - 199.6		0.1 - 2.4		
5-29 y	14.4 - 57.7		0.1 - 0.2		
≥30 y	3.8 - 10.1		0.0		
S. pneumoniae (<18 y only)					
IPD		UR: 3.8		UR: 3.8	[49,63,64]
<1 y	12.0		5.0		
<1-10 y	1.4 - 5.9		0.5 - 2.3		
<11-17 y	0.6		0.3		
Pneumococcal pneumonia hospitalizations[c]		UR: 1.0		UR: 1.0	[65–67]
<11 y	75.7		6.3		
11-17 y	14.2		1.5		
Pneumococcal pneumonia outpatient visits[c]		UR: 1.0		UR: 1.0	[66–69]
<11 y	312.6		26.1		
11-17 y	58.5		6.2		
Pneumococcal AOM[c]	5,368.0 - 9,768.0	UR: 1.0	693.3 - 3,528.9	UR: 1.0	[70–73]
Tetanus		UR: 1.4		UR: 1.0	[46,74,75]
<1 y	0.6		0.0		
1-14 y	0.6		0.0		
≥15 y	0.5 - 7.0		0.0 - 0.3		
Varicella		UR: 1.2		UR: 1.0	[76–78]
<15 y	2,478.0 - 9,969.0		285.0 - 1,146.4		
≥15 y	27.2 - 66.5		2.7 - 6.7		

AOM = acute otitis media; ED = emergency department; IMD = invasive meningococcal disease; IPD = invasive pneumococcal disease; N/A = not applicable; NIP = National Immunization Program; NMA = nonmedically attended; UA = underascertainment; UR = underreporting.

[a]A range indicates that incidence varies by age group within the presented range.

[b]Underestimation is differentiated by UA, where underestimated cases are assumed to be uncomplicated or nonmedically attended, and UR, where underestimated cases are assumed to be medically attended but not reported to the surveillance system. The underestimation factors for hepatitis B (pre-vaccine and vaccine era), measles (pre-vaccine and vaccine era), mumps (pre-vaccine and vaccine era), rubella (pre-vaccine and vaccine era), and varicella (pre-vaccine) were informed by expert opinion, although Ciofi Degli Atti et al. [55] estimated significant underreporting for several pediatric vaccine-preventable diseases in Italy. Underestimation factors were not applicable to NMA rotavirus, as incidence of NMA disease was based on an assumed 32:1 incidence ratio for NMA rotavirus to hospitalized rotavirus [60].

[c]Calculated from all-cause pneumonia and otitis media incidence rates, which were adjusted to account for the percentage of cases that were due to *S. pneumoniae*.

to capture the impact of vaccine-related adverse events on quality of life and the impact of disease on quality of life.

The number of vaccine-related adverse events experienced by the birth cohort was calculated using VCRs and the adverse event rate per 100,000 doses for each vaccine in the Italian pediatric NIP [40] (Supplement Table S2). The total number of QALYs lost due to adverse events was then calculated by multiplying the number of adverse events for each vaccine by the QALY loss per event (Supplement Table S3) and discounting on the basis of the year of vaccination.

For disease-related QALY losses, the model captured the impact of the acute case of illness, long-term complications (where applicable), and disease-related death (where applicable). For the acute case of illness, QALY loss per case was calculated using disease- and severity-specific disutility values and their associated duration of illness to calculate QALYs lost per case; due to the lack of Italy-specific quality-of-life data, these inputs were based on global estimates published in Carrico et al. [20]. For long-term complications following the initial infection that persists for a patient's remaining lifetime, the disutility value was applied each year for the individual's remaining life expectancy based on the age at infection. For lifelong complications that likely shorten life expectancy compared with the average life expectancy in Italy (e.g. neurological deficits following a proportion of meningitis cases or encephalitis cases), we assumed shortened durations of remaining years of life based on the method used in an economic analysis of varicella vaccination in Italy by Thiry and colleagues [27]. This was a conservative approach compared with the previously published analyses of this model in the US, Belgium, and Poland that assumed average remaining life expectancy for individuals with congenital rubella syndrome and individuals with lifelong complications following a case of meningitis or a case of encephalitis [18–20]. For disease-related deaths, QALYs lost were calculated on the basis of the QALE at the age of premature death. All QALY losses were discounted to the time of the analysis using an annual discount rate of 3% [37]. Details on quality-of-life utility values, disutility values, and QALY loss per disease are included in the Supplement (Table S17).

2.5. Direct medical costs

To capture the costs of cases of VPDs, the model multiplied the number of cases of each disease by the cost per case, considering different levels of healthcare resource utilization and/or severity of clinical outcomes. Costs per case included all direct medical costs for diagnosis and treatment of the acute case (i.e. inpatient, outpatient, and/or medication costs where applicable). Costs per case and the probability of clinical outcomes by severity are provided in the Supplement (Tables S4-S16). For some VPDs, nonmedically attended cases were included. Nonmedically attended cases were assumed to have no direct medical cost because medical care was not sought; however, they incurred QALY losses as well as productivity loss costs (for the patient or one caregiver).

For diseases with long-term complications that lead to lifetime disability or management (e.g. encephalitis-related neurological impairment), a probability of complication was applied among survivors of the acute infection and then an annual cost of management of long-term sequelae was applied for the remaining lifetime of the individual affected. Because cases of disease can happen at any age of the modeled birth cohort, the cost of lifetime sequelae management accounted for the age at which infection occurred, age-specific remaining life expectancy based on Italian life tables, and discounting of future costs at 3% per year.

All direct medical costs reflect the cost of care in the current vaccine era in Italy and were reported in 2021 euros, where needed, costs were inflated to 2021 euros [81].

2.6. Productivity losses costs due to disease

The human capital approach was applied to calculate the value of time loss due to acute disease, long-term complications, and disease-related mortality [82]. The annual number of cases of the disease was multiplied by the number of days of productivity loss per case (by severity type) divided by 365; time loss for cases of disease among children was multiplied by an estimated average wage for a caregiver (€90 per day) in Italy [44]. As the cohort aged, productivity losses were multiplied by an age-specific wage of the patient (aged 15–64 years); productivity losses were not included after the cohort was 65 years and older. Time loss estimates per case are provided in the Supplement (Table S18).

Remaining life expectancy at the age of infection or death and age-specific wages were used to calculate discounted productivity losses associated with lifelong complications and disease-related deaths. Similar to discounted lifetime QALY losses for deaths and lifelong complications, the average life expectancy was used as the duration of productivity losses for all disease-related deaths; for those who developed lifelong sequelae, a reduced annual wage and reduced life expectancy (using the method in Thiry and colleagues [27]) were conservatively assumed. Wages for a caregiver or patient in Italy in 2020 and assumptions around reduced annual wages for disabled individuals with lifelong complications are detailed in the Supplement (Tables S19-S20).

2.7. Analyses

All outcomes were calculated for each modeled disease for the two analyses: With NIP and No NIP (i.e. a counterfactual scenario in which the NIP had been discontinued and incidence was to revert to pre-vaccine levels). Outcomes included cumulative cases averted, deaths averted, LYs gained, QALYs gained, and direct and indirect costs averted over the birth cohort's lifetime and were calculated and discounted at 3% each year. For the healthcare-sector perspective, total costs averted were calculated as the discounted cumulative cost of the vaccination program minus discounted lifetime direct medical costs of disease cases averted; for the societal perspective, total costs averted were calculated as vaccination program costs minus discounted lifetime direct and indirect costs of disease cases averted. The BCR of the Italian NIP was then calculated for each perspective by dividing the total costs averted by the vaccination program cost. A classical cost–benefit analysis was not conducted in the base-case analysis,

but an attempt to provide an economic value to QALYs gained was made in a scenario analysis.

2.7.1. Scenario analyses

In addition to base-case analyses, we conducted scenario analyses to assess the robustness of the analysis results to changes in key assumptions across all modeled diseases and/or vaccines. The modeled scenarios considered the following relative variations from base-case input values or analysis settings: (1–2) ± 20% variation in pre-vaccine disease incidence, (3–4) ± 20% variation in vaccine-era disease incidence, (5–6) ± 10% change in vaccination program costs, (7–8) ± 10% change in healthcare-sector disease-related costs, (9–10) ± 10% change in disease case-fatality rates, (11) inclusion of the economic value of QALYs gained in the BCR calculation from the societal perspective (cost–benefit analysis), and (12) exclusion of productivity losses due to disease-related mortality.

3. Results

3.1. Base-case analysis

The Italian pediatric NIP was estimated to have reduced disease incidence from pre-vaccine incidence, ranging from 63% to nearly 100%, with a ≥ 95% reduction in diphtheria, hepatitis B, measles, mumps, pertussis, polio, rubella, and tetanus. Cases of diphtheria, *Haemophilus influenzae* type b, polio, rubella, and tetanus were each reduced to fewer than 100 cases in the lifetime of the birth cohort. Across the VPDs targeted, the NIP was estimated to prevent 1.8 million cases of infections and 3,330 deaths (undiscounted) over the lifetime of the 2020 Italy birth cohort. Vaccination averted the greatest number of cases of varicella (359,500), pneumococcal acute otitis media (351,800), and measles (327,700). Vaccination had the largest impact in averting deaths caused by hepatitis B and diphtheria. When health outcomes were discounted (for use in the cost–benefit analysis), the Italian NIP was estimated to prevent 45,900 LYs lost and 57,000 QALYs lost (Table 3). QALYs lost due to vaccine-related adverse events were negligible.

Pediatric immunization averted €419 million in (discounted) direct medical costs associated with disease cases averted (Figure 1). The breakdown in disease-related cost averted shows that avoided cases of polio and diphtheria led to the greatest cost saving from the healthcare-sector perspective, with these making up 27.2% and 14.8% of all cost savings. From a societal perspective, the greatest cost savings were from avoided cases of diphtheria and hepatitis B (Figure 2).

The NIP was associated with discounted vaccination costs of €251 million (€600 per person in the birth cohort) from the healthcare-sector perspective and €285 million (€680 per person in the birth cohort) from the societal perspective. Vaccination costs over the birth cohort's first 10 years of life were fully offset by the €419 million (€1,000 per person in the birth cohort) and €1.6 billion (€3,830 per person in the birth cohort) in disease-related costs averted over the cohort's lifetime from the healthcare-sector perspective and societal perspective, respectively. Pediatric immunization was associated with €168 million in discounted averted direct medical costs, leading to a BCR of 1.7 from the healthcare-sector perspective; the NIP resulted in €1.3 billion in discounted averted societal costs, leading to a BCR of 5.6 from the societal perspective (Table 4; Figures 1 and 2).

3.2. Scenario analyses

Scenarios that varied the methodological assumptions had the largest impact on societal BCRs (Table 5), as the societal BCR increased from 5.6 in the base-case analysis to 15.6 when the economic value of QALYs gained was included in the BCR calculation, whereas the societal BCR decreased to 2.7 when productivity losses due to disease-related mortality were excluded from the societal perspective.

Among scenarios that varied assumptions for epidemiological and economic input data, BCRs were most sensitive to pre-vaccine incidence, as societal BCRs ranged from 4.5 to 6.8 when pre-vaccine incidence across all diseases was varied by −20% and +20%, respectively (Scenarios 1–2). BCRs were also

Table 3. Health outcomes by disease for with NIP versus No NIP.

Disease	Cases averted (undiscounted)	Deaths averted (undiscounted)	LYs gained	QALYs gained
Diphtheria	5,820	1,160	27,800	26,900
Hepatitis B	22,500	1,490	11,800	15,500
H. influenzae type b	200	4	120	290
IMD (serogroups A, B, C, W, Y)	180	11	230	750
Measles	327,700	50	570	1,440
Mumps	194,600	0	0	700
Pertussis	143,300	80	1,960	3,580
Polio	1,700	34	860	1,150
Rotavirus	267,900	3	90	860
Rubella	73,400	2	45	360
S. pneumoniae[a]	370,500	15	390	2,040
Tetanus	1,180	470	1,870	1,750
Varicella	359,500	6	110	1,680
Total (discounted)	N/A	N/A	45,900	57,000
Total (undiscounted)	1,768,600	3,330	170,000	183,000

IMD = invasive meningococcal disease; LY = life-year; N/A = not applicable; NIP = National Immunization Program; QALY = quality-adjusted life-year.
Note: Life-years and QALYs gained are discounted at 3% per year. Outcomes with values that are greater than 10,000 are rounded to the nearest hundred, whereas values that are greater than 100 but less than 10,000 are rounded to the nearest 10. Totals may not equal the sum of disease-specific outcomes due to rounding.
[a]Outcomes for pneumococcal disease are reported as a sum of cases of invasive pneumococcal disease (IPD) and estimated cases of pneumococcal pneumonia and acute otitis media (AOM). The breakdown of undiscounted cases averted includes 460 cases of IPD 18,300 cases of pneumococcal pneumonia, and 351,800 cases of pneumococcal AOM.

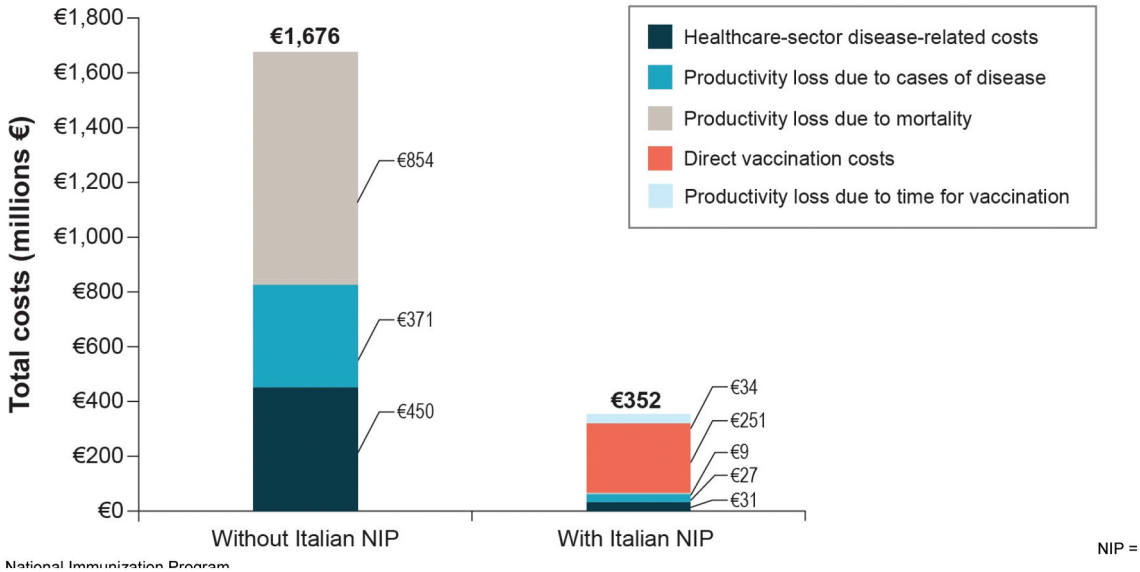

Figure 1. Societal perspective costs with NIP and No NIP by cost type.

NIP = National Immunization Program.

Costs are discounted at 3% per year and presented in 2021 euros. Direct vaccination costs (orange) include vaccine acquisition costs without value added tax, administration costs, adverse event – related costs, and estimates of vaccine wastage; cold-chain supply costs are not included. Indirect costs (light blue) include time for a caregiver to bring a child to be vaccinated; travel costs related to vaccination are not included.

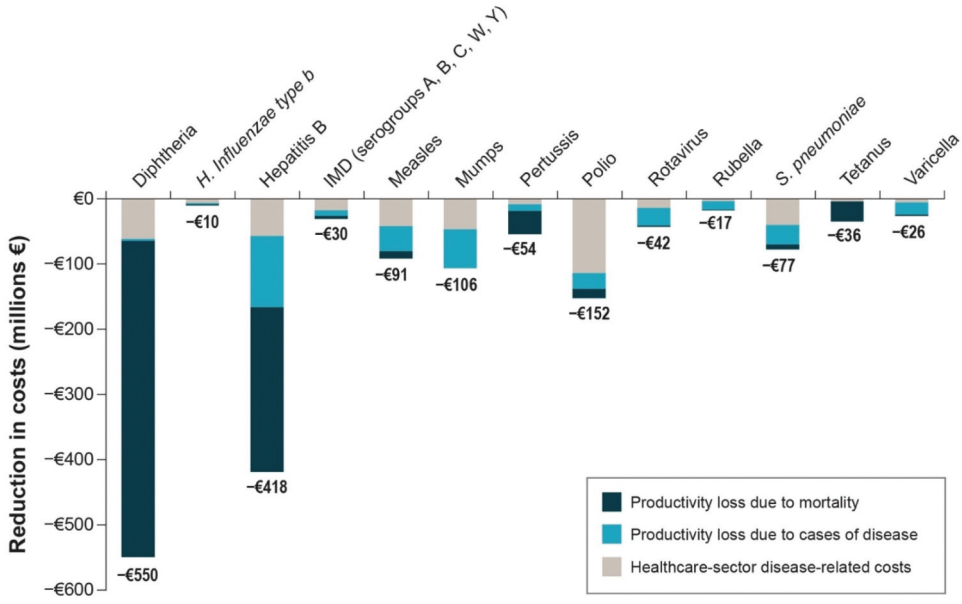

Figure 2. Disease-related costs averted by vaccine-preventable disease.

IMD = invasive meningococcal disease.

Costs are discounted at 3% per year and presented in 2021 euros.

moderately sensitive to variations in vaccination costs, with societal BCRs of 6.3 and 5.1 when total vaccination program costs (acquisition, administration, adverse events, and indirect costs) were varied by −10% and +10%, respectively (Scenarios 5–6). Variation in vaccine-era incidence, healthcare-sector disease-related costs, and disease case-fatality rates only minorly impacted societal BCRs for the NIP (societal BCR changed by ≤0.3). The NIP remained cost saving (i.e. BCRs remained above 1) from the healthcare-sector and societal perspectives in all scenarios.

4. Discussion

Our study estimated that the pediatric NIP in Italy would prevent 1.8 million cases of infections, 3,330 deaths 45,900 LYs lost (discounted), and 57,000 QALYs lost (discounted) over

Table 4. Cost–benefit analysis for the Italian NIP compared with no NIP.

Incremental outcome	Healthcare-sector perspective (€ millions)	Societal perspective (€ millions)
Vaccination program costs	251.1	285.1
Acquisition	214.8	214.8
Administration	36.2	36.2
Adverse events	0.1	0.1
Productivity loss (time loss) for vaccination	N/A	34.1
Disease-related costs averted	419.5	1,609.0
Disease treatment	419.5	419.5
Productivity loss due to disease	N/A	344.1
Productivity loss due to disease-related mortality	N/A	845.4
Total costs averted[a]	168.4	1,323.8
Benefit-cost ratio	1.7	5.6

N/A = not applicable; NIP = National Immunization Program.
Note: costs are discounted at 3% per year and presented in 2021 euros.
[a]Costs averted may not equal disease-related costs averted minus vaccination program costs exactly due to rounding.

Table 5. Scenario analysis results.

Scenario	Healthcare-sector BCR	Societal BCR
Base case	1.7	5.6
Scenario 1: 20% increase in pre-vaccine incidence	2.0	6.8
Scenario 2: 20% reduction in pre-vaccine incidence	1.3	4.5
Scenario 3: 20% increase in vaccine-era incidence	1.6	5.6
Scenario 4: 20% reduction in vaccine-era incidence	1.7	5.7
Scenario 5: 10% increase in vaccination program costs	1.5	5.1
Scenario 6: 10% reduction in vaccination program costs	1.9	6.3
Scenario 7: 10% increase in healthcare-sector disease-related costs	1.8	5.8
Scenario 8: 10% reduction in healthcare-sector disease-related costs	1.5	5.5
Scenario 9: 10% increase in case-fatality rates	1.7	5.9
Scenario 10: 10% reduction in case-fatality rates	1.7	5.4
Scenario 11: inclusion of the economic value of QALYs gained in the BCR calculation (societal perspective only)	N/A	15.6
Scenario 12: Exclusion of productivity losses due to disease-related mortality	1.7	2.7

BCR = benefit–cost ratio; N/A = not applicable; QALY = quality-adjusted life-year.

the lifetime of the 2020 Italian birth cohort. Continued investment in the vaccination program year over year is estimated to result in a net savings of €1.3 billion, with a BCR of 5.6 from a societal perspective, which translates to a return on investment of €5.6 to society for every €1 spent.

This study is the first to our knowledge to evaluate the return on investment of the Italian NIP, including all mandatory and recommended pediatric vaccines as of 2019. BCRs estimated for the Italian NIP were within the range of BCRs estimated in Belgium and Poland using the same modeling framework [18,19]. One previous study estimated the impact of immunization on population-level morbidity and mortality from 10 VPDs in Italy through 2015 [83]. Relative reductions in disease cases estimated in our study were higher than estimates from Pezzotti and colleagues (Supplement Table S22), which accounted for temporal trends in disease activity prior to vaccine introduction and did not attempt to adjust disease incidence estimates for underdiagnosis or underreporting. Notably, Pezzotti and colleagues estimated only a 42% reduction in varicella cases after vaccine introduction, as the analysis timeframe preceded mandatory vaccine recommendations and population-level vaccine coverage was, therefore, low at 30% [83]. In our study, where coverage for varicella-containing vaccine was estimated to be over 90%, relative case reduction was estimated to be 90% based on observed vaccine effectiveness in Italy [78,84]. The study by Pezzotti and colleagues also did not estimate the impacts of pediatric immunization on *Haemophilus influenzae* type b, RV, or *S. pneumoniae*; reductions in incidence after introduction of these vaccines were estimated to be substantial in our study (93%, 74%, and 77% reductions in *Haemophilus influenzae* type b, RV, and *S. pneumoniae* incidence, respectively).

The BCR, our primary measure of return on investment in this study, differed substantially between the healthcare-sector perspective (where only direct medical costs were considered) and the societal perspective. This difference is aligned with our findings in other countries, where productivity losses due to morbidity and mortality from averted cases of disease account for a large portion of the savings in costs [18–20]. Consistent with previous economic evaluations of immunization programs, we used the human capital approach to estimate productivity losses, which typically estimates larger productivity losses than alternate approaches, such as the friction cost method [18–20,22,85]. Although Italian economic evaluation guidelines discuss the societal perspective, they do not specify what approach should be used for valuing productivity losses and gains [86]. We conservatively only included market productivity losses for individuals less than 65 years of age, including market productivity loss for this age group, as well as the value of nonmarket productivity for all ages [87,88], would have led to a higher BCR. To address the model's sensitivity to productivity loss costs, we conducted scenario analyses excluding productivity loss costs resulting from death. In this scenario, the BCR decreased from 5.6 to 2.7,

highlighting the sensitivity of our results to deaths averted. Although sensitive to these productivity loss costs, these results demonstrate the public health impact of the Italian NIP in preventing both morbidity and early mortality as well as the sustained value of the NIP even when indirect costs are excluded from the analysis.

Although BCR was the primary outcome measure, no attempt was made in the base-case analysis to quantify the economic value of QALYs gained with NIP. However, in a scenario analysis, it was estimated that, assuming a willingness to pay of €50,000 per QALY, the BCR increased from 5.6 to 15.6, emphasizing the impact of the NIP in reducing mortality and morbidity. Despite the large uncertainty in both pre-vaccine incidence and underestimation factors, scenario analysis found that the BCR was relatively insensitive to wide ranges of incidence tested across all modeled diseases (range for societal BCR: 4.5–6.8).

A strength of our analysis was using pre-vaccine and current-day incidence data based on observed reductions in incidence of disease. This framework allowed for fewer assumptions around vaccine efficacy and herd immunity for each individual vaccine; however, it did require other assumptions (primarily around pre-vaccine incidence and data gaps or limitations for diseases that are nearly or fully eradicated in Italy). The analysis did not control for other temporal factors (e.g. other public health improvements) that may have contributed to reduced disease morbidity and mortality, nor did it account for the extended benefits of vaccination, including macroeconomic benefits, advances in health equity, and reductions in antimicrobial resistance [89,90]. In addition, the analysis did not account for regional immunization offers prior to the 2017–2019 NIP, or for the possibility that some regions, having adopted certain vaccinations before the NIP release, may benefit from higher BCRs than others with less rigorous immunization schedules and lower vaccine uptake.

This model framework did not allow for separately estimating the impact of the pediatric NIP, adolescent/adult booster vaccines (i.e. MenACWY booster, Tdap booster), and adult vaccines (i.e. PCV-13) in reducing incidence of disease over a person's lifetime. To remedy this structural limitation with our objective of estimating the return on investment and BCR of the pediatric NIP, incidence of *S. pneumoniae* for ages >10 years was excluded from the analysis; this is conservative in terms of the BCR because reduction in disease is likely due to both adult pneumoccal vaccination in Italy and herd effects of pediatric vaccination. The impact on disease control for diphtheria, tetanus, pertussis, and meningococcus was determined by experts to be mostly attributable to the pediatric NIP, with acknowledgment that our analysis likely slightly overestimates the BCR by not accounting for the cost of adolescent/adult booster doses.

An important limitation of this study was the challenge around data availability. Pre-vaccine incidence for diseases where routine vaccination pre-dated modern surveillance systems in Italy led to concerns about the quality and possible low reliability of data. To account for this, care was taken in considering the difficulty in estimating true incidence, both pre-vaccines and in the vaccine era. We applied an underestimation factor to adjust incidence for diseases that are known to suffer from underreporting and/or underascertainment using expert opinion; in the case of invasive pneumococcal disease, incidence was adjusted using recently published estimates of underreporting in Italy [64]. Although adjusted incidence introduced additional assumptions to our study, we validated our model projections to confirm that the underestimation factors did not lead to nonsensical results for VPDs where a primary infection can occur only once in a person's lifetime (e.g. varicella zoster virus, hepatitis B). We believe this undertaking to adjust the pre-vaccine and post-vaccine incidence for underestimation led to more realistic estimates of incidence compared with relying on data from surveillance systems and led to an extension of previous studies that excluded diseases with known underreporting [83]. Another data limitation was that current disease management cost estimates, particularly for high-severity cases, were limited or unavailable for diseases that are nearly or fully eradicated in Italy. Thus, Italian hospitalization costs for related diagnosis-related group codes were used as proxies for some severe disease case costs (e.g. diphtheria, tetanus), whereas other costs were obtained from other countries (e.g. polio costs were obtained from Belgium and converted to Italian currency, accounting for purchasing power parity).

Finally, our analysis focused on the 2017–2019 NIP, but the 2023–25 Italian NIP [16] was recently released with important changes, including a shift from MenC to MenACWY vaccine. Our analysis included the MenACWY vaccine at age 13 months (replacing MenC at the same age) because regional uptake of this vaccine has shown to be strong. In fact, many Italian regions started to offer (free of charge or with a copayment) at the regional level the quadrivalent MenACWY vaccine even before the release of the current 2023–25 NIP. Nevertheless, vaccination coverage at age 24 months for the MenACWY vaccine is lower than that reported for the monovalent MenC vaccine at the national level, likely resulting in an underestimate of population-level meningococcal vaccine coverage and subsequent vaccination costs. On the other hand, the cost of the quadrivalent MenACWY vaccine is higher than that of the monovalent MenC vaccine, which may compensate for the underestimation in population-level coverage in our analysis. Other recent updates to the NIP (e.g. seasonal influenza vaccine recommendation and reduction from four to three doses of Men B vaccine) were out of the scope of this analysis, as it is too early in the implementation of recent updates to assess their impact. This analysis did not consider costs related to infectious disease outbreaks where there are direct medical and nonmedical costs incurred for reporting and responding to such outbreaks. This was out of the scope of the analysis but could be an important area of future research on the economic costs related to outbreaks from VPDs, such as measles outbreaks in Italy, and the importance of mandatory vaccination to prevent outbreaks and the reemergence of VPDs [91].

5. Conclusions

The Italian pediatric NIP brings large-scale prevention of disease-related morbidity, mortality, and associated costs over

the lifetime with a positive return on investment for the national health system and for society. This highlights the value of continued investment in pediatric immunization and the importance of sustained population-level vaccination coverage to maintain the positive public health and economic impact of the NIP.

Acknowledgments

Kate Lothman of RTI Health Solutions provided medical writing support for the development of this manuscript. These services were funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Author contribution statement

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure statement

S Talbird, J Carrico, and C Mellott are employed (or were employed at the time of the analysis) by RTI Health Solutions, which received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, for the conduct of this study. M Barbieri is a Health Economist who has received a grant from MSD Italy to conduct this analysis. F Senese is an employee of MSD Italy and owns stock in Merck & Co., Inc., Rahway, NJ, USA. JC Lang is an employee of Merck Canada Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and holds stock in Merck & Co., Inc., Rahway, NJ, USA. G Bencina is an employee of MSD, Spain, Madrid, and owns stock in Merck & Co., Inc., Rahway, NJ, USA. P Bonanni, A Bechini, and S Boccalini have received personal consulting fees for assessment of input data. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Funding

The manuscript was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Data availability statement

Data are available within the article and its supplementary materials.

Reviewer disclosures

A peer reviewer on this manuscript has disclosed that they receive speaking and lecture fees from Pfizer, Sanofi, GSK, and Moderna. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. World Health Organization [Internet]. The case for investing in public health. 2014 [cited 2021 Aug 24]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0009/278073/Case-Investing-Public-Health.pdf
2. World Health Organization [Internet]. WHO guide for standardization of economic evaluations of immunization programmes. 2019 [cited 2024 Aug 1]. Available from: https://iris.who.int/bitstream/handle/10665/329389/WHO-IVB-19.10-eng.pdf
3. Mauskopf J, Standaert B, Connolly MP, et al. Economic analysis of vaccination programs: an ISPOR good practices for outcomes research task force report. Value Health. 2018;21(10):1133–1149. doi: 10.1016/j.jval.2018.08.005
4. Jit M, Hutubessy R, Png ME, et al. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. BMC Med. 2015;13(1):209. doi: 10.1186/s12916-015-0446-9
5. Annemans L, Beutels P, Bloom DE, et al. Economic evaluation of vaccines: Belgian reflections on the need for a broader perspective. Value Health. 2021;24(1):105–111. doi: 10.1016/j.jval.2020.09.005
6. Barbieri M, Boccalini S. Return on investment (ROI) of three vaccination programmes in Italy: HPV at 12 years, herpes zoster in adults, and influenza in the elderly. Vaccines (Basel). 2023;11(5):924. doi: 10.3390/vaccines11050924
•• **Describes return on investment for the Italian vaccination program in adults.**
7. Ministero della Salute [Internet]. Piano nazionale vaccini 1999-2000. 1999 Jun 18 [cited 2024 May 10]. Available from: https://www.salute.gov.it/imgs/C_17_pubblicazioni_77_allegato.pdf
8. Signorelli C. Forty years (1978-2018) of vaccination policies in Italy. Acta Biomed. 2019;90(1):127–133. doi: 10.23750/abm.v90i1.7900
9. Ministero della Salute [Internet]. Piano nazionale prevenzione vaccinale 2012–2014. 2012-2014 [cited 2024 Mar 15]. Available from: https://www.salute.gov.it/imgs/C_17_pubblicazioni_1721_allegato.pdf
10. Ministero della Salute [Internet]. Conversione in legge, con modificazioni, del decreto-legge 7 giugno 2017, n. 73, recante disposizioni urgenti in materia di prevenzione vaccinale. (17G00132). Legge 31 luglio 2017, n. 119. G.U. Serie Generale, n. 182 del 05 agosto 2017. 2017 [cited 2024 Aug 2]. Available from: https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=60201
11. Signorelli C, Guerra R, Siliquini R, et al. Italy's response to vaccine hesitancy: an innovative and cost effective national immunization plan based on scientific evidence. Vaccine. 2017;35(33):4057–4059. doi: 10.1016/j.vaccine.2017.06.011
12. Signorelli C, Odone A, Ricciardi W, et al. The social responsibility of public health: Italy's lesson on vaccine hesitancy. Eur J Public Health. 2019;29(6):1003–1004. doi: 10.1093/eurpub/ckz135
13. D'Ancona F, D'Amario C, Maraglino F, et al. The law on compulsory vaccination in Italy: an update 2 years after the introduction. Euro Surveill. 2019;24(26). doi: 10.2807/1560-7917.ES.2019.24.26.1900371
14. Ministero della Salute [Internet]. Piano nazionale prevenzione vaccinale 2017-2019. 2017-2019 [cited 2024 Mar 15]. Available from: https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?id=2571
15. ECDC [Internet]. Diphtheria: annual epidemiological report for 2017. European centre for disease prevention and control. 2019 Jun [cited 2021 Oct 28]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/diphtheria-annual-epidemiological-report-2017.pdf
16. Ministero della Salute [Internet]. Intesa, ai sensi dell'articolo 8, comma 6, della legge 5 giugno 2003, n. 131, tra il Governo, le regioni e le Province autonome di Trento e di Bolzano, sul documento recante "Piano nazionale di prevenzione vaccinale (PNPV) 2023-2025" e sul documento recante "Calendario nazionale vaccinale". 2023 Aug 2 [cited 2024 May 10]. Available from: https://www.trovanorme.salute.gov.it/norme/dettaglioAtto.spring?id=95963&page=newsett
17. Bencina G, Bento-Abreu A, Sabale U, et al. Estimating the lifetime cost of vaccination in 23 European countries: a modeling study. Expert Rev Vaccines. 2023;22(1):148–160. doi: 10.1080/14760584.2023.2157266
•• **Estimates lifetime vaccination costs in European countries.**

18. Carrico J, Mellott CE, Talbird SE, et al. Public health impact and return on investment of Belgium's pediatric immunization program. Front Public Health. 2023;11:1032385. doi: 10.3389/fpubh.2023.1032385
- **Describes a similar analysis conducted in Belgium.**
19. Mellott CE, Jaworski R, Carrico J, et al. Public health impact and return on investment of the pediatric immunization program in Poland. Expert Rev Vaccines. 2023;22(1):1114–1125. doi: 10.1080/14760584.2023.2275712
- **Describes a similar analysis conducted in Poland.**
20. Carrico J, La EM, Talbird SE, et al. Value of the immunization program for children in the 2017 US birth cohort. Pediatric. 2022;150(3):e20210560. doi: 10.1542/peds.2021-056007
- •• **Describes in detail the model structure and approach used in this analysis.**
21. Zhou F, Santoli J, Messonnier ML, et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. Arch Pediatr Adolesc Med. 2005;159(12):1136–1144. doi: 10.1001/archpedi.159.12.1136
22. Zhou F, Shefer A, Wenger J, et al. Economic evaluation of the routine childhood immunization program in the United States, 2009. Pediatric. 2014;133(4):577–585. doi: 10.1542/peds.2013-0698
23. Calabro GE, Vitale F, Rizzo C, et al. The new 15-valent pneumococcal conjugate vaccine for the prevention of S. pneumoniae infections in pediatric age: a health technology assessment. J Prev Med Hyg. 2023;64(1 Suppl 1):E1–E160.
24. Gasparini R, Landa P, Amicizia D, et al. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero®) against meningococcal B disease: a cost-effectiveness analysis. Hum Vaccin Immunother. 2016;12(8):2148–2161. doi: 10.1080/21645515.2016.1160177
25. Ansaldi F, Pugh S, Amicizia D, et al. Estimating the clinical and economic impact of switching from the 13-valent pneumococcal conjugate vaccine (PCV13) to the 10-valent pneumococcal conjugate vaccine (PCV10) in Italy. Pathogens. 2020;9(2):76. doi: 10.3390/pathogens9020076
26. Giammanco MD, Coniglio MA, Pignato S, et al. An economic analysis of rotavirus vaccination in Italy. Vaccine. 2009;27(29):3904–3911. doi: 10.1016/j.vaccine.2009.04.002
27. Thiry N, Beutels P, Tancredi F, et al. An economic evaluation of varicella vaccination in Italian adolescents. Vaccine. 2004;22(27–-28):3546–3562. doi: 10.1016/j.vaccine.2004.03.043
28. Azzari C, Baldo V, Giuffrida S, et al. The cost-effectiveness of universal varicella vaccination in Italy: a model-based assessment of vaccination strategies. Clinicoecon Outcomes Res. 2020;12:273–283. doi: 10.2147/CEOR.S229685
29. Boccalini S, Taddei C, Ceccherini V, et al. Economic analysis of the first 20 years of universal hepatitis B vaccination program in Italy: an a posteriori evaluation and forecast of future benefits. Hum Vaccin Immunother. 2013;9(5):1119–1128. doi: 10.4161/hv.23827
30. Boccalini S, Pariani E, Calabrò GE, et al. Health technology assessment (HTA) of the introduction of influenza vaccination for Italian children with fluenz tetra(®). J Prev Med Hyg. 2021;62(2 Suppl 1):E1–e118.
31. ECDC. Seasonal influenza vaccination recommendations and coverage rates in EU/EEA member states: an overview of vaccination recommendations for 2021–22 and coverage rates for the 2018–19 to 2020–21 influenza seasons. 2023 [cited 2024 Mar 20]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Seasonal_flu_vacc_recs_and_coverage_rates_EU_EEA.pdf
32. D'Ambrosio F, Lanza TE, Messina R, et al. Influenza vaccination coverage in pediatric population in Italy: an analysis of recent trends. Ital J Pediatr. 2022;48(1):77. doi: 10.1186/s13052-022-01271-0
33. ISTAT [Internet]. ISTATdemo. Istituto Nazionale di Statistica. 2020 [cited 2023 Apr 21]. Available from: http://dati.istat.it/Index.aspx
34. Ministero della Salute [Internet]. Coperture età pediatrica a 24 mesi: Anno 2019 (coorte 2017). 2019 [cited 2023 Apr 21]. Available from: https://www.salute.gov.it/imgs/C_17_bancheDati_38_3_0_file.pdf
35. Ministero della Salute [Internet]. Coperture età pediatrica a 24 mesi: Anno 2020 (coorte 2018). 2020 [cited 2024 Mar 28]. Available from: https://www.salute.gov.it/imgs/C_17_tavole_20_9_0_file.pdf
36. Istituto Superiore di Sanità [Internet]. Italian immunization schedule. [cited 2024 Mar 15]. Available from: https://www.epicentro.iss.it/en/vaccines/immunization-schedule-italy
37. Fiorentino F, Urbinati D. First Italian guidelines for the economic evaluation of health technologies: how do they compare to NICE standards? GIHTAD. 2021;14(5).
38. AIFA [Internet]. Report OSMED interactive. Price per DDD. Agenzia Italiana del Farmaco. 2020 [cited 2023 Apr 21]. Available from: https://www.aifa.gov.it/en/osmed-interattivo
39. SISAC [Internet]. Family pediatricians dn GPs national contract. Struttura Interregionale Sanitari Convenzionati. 2005 [cited 2023 Apr 21]. Available from: https://www.sisac.info/aree/www.sisac.info/resources/MEDICINA_GENERALE/ACN_testo_integrato.pdf
40. AIFA [Internet]. Rapporto vaccini 2019. La sorveglianza postmarketing in Italia. Agenzia Italiana del Farmaco. 2019 [cited 2023 Apr 21]. Available from: https://sip.it/wp-content/uploads/2020/12/Rapporto-AIFA-Vaccini-2019.pdf
41. Esposito S, Cantarutti L, Molteni CG, et al. Clinical manifestations and socio-economic impact of influenza among healthy children in the community. J Infect. 2011;62(5):379–387. doi: 10.1016/j.jinf.2011.02.015
42. Di Minno G, Ravasio R. Cost-effectiveness analysis of caplacizumab in the new standard of care for immune thrombotic thrombocytopenic purpura in Italy. GRHTA. 2021;8(1):43–52. doi: 10.33393/grhta.2021.2191
43. Gazzetta Ufficiale della Repubblica Italiana. Remunerazione delle prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale. 2013.
44. JP SALARY OUTLOOK [Internet]. L'analisi del mercato retributivo italiano. 2020 [cited 2024 Aug 1]. Available from: https://jpcondivisi.s3.eu-west-1.amazonaws.com/Whitepaper-guide+e+altri+documenti+/Up+to+date/JP+Salary+Outlook_ed_I.pdf
45. EpiCentro [Internet]. "I vaccini? Funzionano!": settimana europea, e mondiale, delle vaccinazioni 2017. Uno sguardo ragionato allo stato dell'arte delle vaccinazioni in Italia. Istituto Superiore di Sanità. 2017 Apr 20 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/vaccini/SettimanaVaccinazioni2017
46. ECDC Data Atlas [Internet]. Surveillance atlas of infectious diseases. European centre for disease prevention and control. 2020 [cited 2023 Apr 21]. Available from: https://atlas.ecdc.europa.eu/public/index.aspx
47. Monaco M, Mancini F, Ciervo A, et al. La difterite: èancora una malattia da sorvegliare? Not Ist Super Sanità. 2015;28(3):3–8.
48. Ciofi Degli Atti M, Cerquetti M. Le infezioni invasive da Haemophilus influenzae: la situazione italiana dal 1998 al 2003 [Internet]. 2003 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/ben/2004/ottobre/2
49. Istituto Superiore di Sanità [Internet]. Sorveglianza delle malattie batteriche invasive in Italia. 2020 Nov [cited 2023 Apr 21]. Available from: https://www.iss.it/documents/20126/0/Rapporto+consolidato+MIB+2019.pdf/1faeb457-9859-f800-b9aa-bf8aea405093?t=1612517562338
50. Squarcione S, Pompa MG, D'Alessandro D. National surveillance system and hib meningitis incidence in Italy. Eur J Epidemiol. 1999;15(7):685–686. doi: 10.1023/A:1007670904487
51. Mele A, Tosti ME, Spada E, et al. Sistema Epidemiologico Integrato dell'Epatite Virale Acuta (SEIEVA). Rapporto 2000-2001. Istituto Superiore di Sanità [Internet]. 2003 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/epatite/pdf/epatiti.pdf
52. ISIstituto Superiore di Sanità [Internet]. SEIVA bulletin. 2022 [cited 2023 Jul 19]. Available from: https://www.epicentro.iss.it/epatite/bollettino/bollettino-n-11-novembre-2022.pdf
53. Azzari C, Nieddu F, Moriondo M, et al. Underestimation of invasive meningococcal disease in Italy. Emerg Infect Dis. 2016;22(3):469–475. doi: 10.3201/eid2203.150928

54. Filia A. Morbillo: aspetti epidemiologici [Internet]. EpiCentro. 2022 Dec 15 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/morbillo/epidemiologia-italia
55. Ciofi degli Atti ML, Salmaso S, Bella A, et al. Pediatric sentinel surveillance of vaccine-preventable diseases in Italy. Pediatr Infect Dis J. 2002;21(8):763–768. doi: 10.1097/00006454-200208000-00013
56. Ministero della Salute [Internet]. Vaccinazioni, stato dell'arte, falsi miti e prospettive. 2017 Mar 27 [cited 2023 Apr 21]. Available from: https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?id=2586
57. Donzelli A, Bellavite P, Demicheli V. Epidemiology of pertussis and prevention strategies: problems and perspectives. Epidemiol Prev. 2019;43(1):83–91. doi: 10.19191/EP19.1.A001
58. Binkin NJ, Salmaso S, Tozzi AE, et al. Epidemiology of pertussis in a developed country with low vaccination coverage: the Italian experience. Pediatr Infect Dis J. 1992;11(8):653–661.
59. Restivo V, Caracci F, Sannasardo CE, et al. Rotavirus gastroenteritis hospitalization rates and correlation with rotavirus vaccination coverage in Sicily. Acta Biomed. 2018;89(3):437–442. doi: 10.23750/abm.v89i3.7578
60. Soriano-Gabarró M, Mrukowicz J, Vesikari T, et al. Burden of rotavirus disease in European Union countries. SPediatr Infect Dis J. 2006;25(1):S7–S11. doi: 10.1097/01.inf.0000197622.98559.01
61. Giambi C [Internet]. Situazione epidemiologica della rosolia congenita in Italia. Istituto Superiore di Sanità. 2013 Apr 17 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/vaccini/pdf/aprile2013/2/GIAMBI_Roslia_congenita_20130417_def.pdf
62. EpiCentro [Internet]. Rosolia congenita e in gravidanza News: il bollettino semestrale. Istituto Superiore di Sanità. 2018 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/rosolia/bollettino
63. D'Ancona F, Caporali MG, Del Manso M, et al. Invasive pneumococcal disease in children and adults in seven Italian regions after the introduction of the conjugate vaccine, 2008-2014. Epidemiol Prev. 2015;39(4 Suppl 1):134–138.
64. Quattrone F, Donzelli G, D'Arienzo S, et al. Invasive pneumococcal disease in tuscany region, Italy, 2016–2017: integrating multiple data sources to investigate underreporting. Int J Environ Res Public Health. 2020;17(20):7581. doi: 10.3390/ijerph17207581
65. Boccalini S, Varone O, Chellini M, et al. Hospitalizations for pneumonia, invasive diseases and otitis in Tuscany (Italy), 2002-2014: which was the impact of universal pneumococcal pediatric vaccination? Hum Vaccin Immunother. 2017;13(2):428–434. doi: 10.1080/21645515.2017.1264796
66. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of streptococcus pneumoniae and haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Glob Health. 2018;6(7):e744–e757. doi: 10.1016/S2214-109X(18)30247-X
67. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372(9):835–845. doi: 10.1056/NEJMoa1405870
68. Viegi G, Pistelli R, Cazzola M, et al. Epidemiological survey on incidence and treatment of community acquired pneumonia in Italy. Respir Med. 2006;100(1):46–55. doi: 10.1016/j.rmed.2005.04.013
69. Sterrantino C, Trifirò G, Lapi F, et al. Burden of community-acquired pneumonia in Italian general practice. Eur Respir J. 2013;42(6):1739–1742. doi: 10.1183/09031936.00128713
70. Marchisio P, Cantarutti L, Sturkenboom M, et al. Burden of acute otitis media in primary care pediatrics in Italy: a secondary data analysis from the pedianet database. BMC Pediatr. 2012;12(1):185. doi: 10.1186/1471-2431-12-185
71. Barbieri E, Porcu G, Hu T, et al. A retrospective database analysis to estimate the burden of acute otitis media in children aged <15 years in the Veneto region (Italy). Children (Basel). 2022 Mar 19;9(3):436. doi: 10.3390/children9030436
72. Barbieri E, Porcu G, Petigara T, et al. The economic burden of pneumococcal disease in children: a population-based investigation in the veneto region of Italy. Children (Basel). 2022;9(9):1347. doi: 10.3390/children9091347
73. Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. Pediatr. 2017;140(3). doi: 10.1542/peds.2017-0181
74. EpiCentro [Internet]. Epidemiologia del tetano in Italia. Istituto Superiore di Sanità. 2002 [cited 2023 Apr 21]. Available from: https://www.epicentro.iss.it/ben/2002/marzo02/2
75. Istituto Centrale di Statistica [Internet]. Annuario di statistiche sanitarie. 1963 [cited 2023 Apr 21];VI - 1960. Available from: https://ebiblio.istat.it/digibib/Sanita/TO00013527StatSanVol061960.pdf
76. Pozza F, Piovesan C, Russo F, et al. Impact of universal vaccination on the epidemiology of varicella in Veneto, Italy. Vaccine. 2011;29(51):9480–9487. doi: 10.1016/j.vaccine.2011.10.022
77. Boccalini S. Valutazione economica della vaccinazione anti-varicella neibambini e adolescenti italiani secondo differenti strategie diintervento: il peso dei casi ospedalizzati non complicati. 2005.
78. Giaquinto C, Gabutti G, Baldo V, et al. Impact of a vaccination programme in children vaccinated with ProQuad, and ProQuad-specific effectiveness against varicella in the Veneto region of Italy. BMC Infect Dis. 2018;18(1):103. doi: 10.1186/s12879-018-3017-9
79. Gibbons CL, Mangen MJ, Plass D, et al. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC Publ Health. 2014;14(1):147. doi: 10.1186/1471-2458-14-147
80. Szende A, Janssen B, Cabases J, editors. Self-reported population health: an international perspective based on EQ-5D. Dordrecht (NL): Springer; 2014.
81. Eurostat [Internet]. HICP - inflation rate. 2023 [cited 2023 Apr 21]. Available from: https://ec.europa.eu/eurostat/databrowser/view/tec00118/default/table?lang=en
82. Weisbrod BA. The valuation of human capital. J Polit Economy. 1961;69(5):425–436. doi: 10.1086/258535
83. Pezzotti P, Bellino S, Prestinaci F, et al. The impact of immunization programs on 10 vaccine preventable diseases in Italy: 1900-2015. Vaccine. 2018;36(11):1435–1443. doi: 10.1016/j.vaccine.2018.01.065
84. Pieri L, Porchia BR, Pieralli F, et al. Assessment of the effectiveness of the universal varicella vaccination program in toscana (Italy), in the period 2010-2013. Epidemiol Prev. 2015;39(4 Suppl 1):119–123.
85. Ozawa S, Clark S, Portnoy A, et al. Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001-2020. Bull World Health Organ. 2017;95(9):629–638. doi: 10.2471/BLT.16.178475
86. AIFA [Internet]. Linea guida per la compilazione del Dossier a supporto della domanda di rimborsabilità e prezzo di un medicinale. 2020 [cited 2024 Mar 20]. Available from: https://www.aifa.gov.it/en/linea-guida-capitolo-9
87. Bloom DE, Khoury A, Algur E, et al. Valuing productive non-market activities of older adults in Europe and the US. De Economist. 2020;168(2):153–181. doi: 10.1007/s10645-020-09362-1
88. Grosse SD, Krueger KV, Pike J. Estimated annual and lifetime labor productivity in the United States, 2016: implications for economic evaluations. J Med Econ. 2019;22(6):501–508. doi: 10.1080/13696998.2018.1542520
89. Postma M, Biundo E, Chicoye A, et al. Capturing the value of vaccination within health technology assessment and health economics: country analysis and priority value concepts. Vaccine. 2022;40(30):3999–4007. doi: 10.1016/j.vaccine.2022.04.026
90. Beck E, Biundo E, Devlin N, et al. Capturing the value of vaccination within health technology assessment and health economics: literature review and novel conceptual framework. Vaccine. 2022;40(30):4008–4016. doi: 10.1016/j.vaccine.2022.04.050
91. Siani A. Measles outbreaks in Italy: a paradigm of the re-emergence of vaccine-preventable diseases in developed countries. Prev Med. 2019;121:99–104. doi: 10.1016/j.ypmed.2019.02.011