



HAL
open science

Estimation of mid-and long-term benefits and hypothetical risk of Guillain-Barre syndrome after human papillomavirus vaccination among boys in France: A simulation study

Chi-Hong Duong, Judith E. Mueller, Pascale Tubert-Bitter, Sylvie Escolano

► **To cite this version:**

Chi-Hong Duong, Judith E. Mueller, Pascale Tubert-Bitter, Sylvie Escolano. Estimation of mid-and long-term benefits and hypothetical risk of Guillain-Barre syndrome after human papillomavirus vaccination among boys in France: A simulation study. *Vaccine*, 2022, 40 (2), pp.359-363. 10.1016/j.vaccine.2021.11.046 . hal-03615470

HAL Id: hal-03615470

<https://ehesp.hal.science/hal-03615470>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Estimation of mid-and long-term benefits and hypothetical risk of Guillain-Barre Syndrome after Human Papillomavirus vaccination among boys in France: a simulation study

Authors: Chi-Hong Duong, Judith E. Mueller, Pascale Tubert-Bitter, Sylvie Escolano

- Chi-Hong Duong
Université Paris-Saclay, UVSQ, Université Paris-Sud, Inserm, High-Dimensional Biostatistics for Drug Safety and Genomics, CESP, Villejuif, France
hong.duong@inserm.fr
- Judith E. Mueller
EHESP French School of Public Health, Paris and Rennes
Institut Pasteur, Paris
judith.mueller@ehesp.fr
- Pascale Tubert-Bitter
Université Paris-Saclay, UVSQ, Université Paris-Sud, Inserm, High-Dimensional Biostatistics for Drug Safety and Genomics, CESP, Villejuif, France
pascale.tubert@inserm.fr
- Sylvie Escolano
Université Paris-Saclay, UVSQ, Université Paris-Sud, Inserm, High-Dimensional Biostatistics for Drug Safety and Genomics, CESP, Villejuif, France
sylvie.escolano@inserm.fr

1 **Background:** The burden of human papillomavirus (HPV) infection can be substantially
2 reduced through vaccination of girls, and gender-neutral policies are being adopted in many
3 countries to accelerate disease control among women and expand direct benefits to men.
4 Clinical direct benefit of boys HPV vaccination has been established for ano-genital warts and
5 anal cancer. HPV vaccines are considered safe, but an association with Guillain-Barre
6 syndrome has been found in French reimbursement and hospital discharge data.

7 **Methods:** We conducted a Monte-Carlo simulation assuming a stable French population of
8 11- to 14-year-old boys, adult men and men having sex with men. We modelled and
9 quantified the mid-term benefits as the annually prevented ano-genital warts among the
10 8.72M men aged 15-35 years and the long-term benefits as the annually prevented anal
11 cancer cases among the 17.4M men aged 25-65 years. We also estimated the number of
12 Guillain-Barre syndrome cases hypothetically induced by vaccination.

13 **Results:** With a vaccine coverage of 30%, an annual number of 9310 (95% uncertainty
14 interval [7050-11200]) first ano-genital warts episodes among the 8.72M men aged 15-35
15 years are prevented. According to more or less optimistic hypotheses on the proportion of
16 HPV cancers covered by the vaccine, between 15.1 [11.7-17.7] and 19.2 [15.0-22.6] cases of
17 anal cancer among the 17.4M men aged 25-65 years would be annually avoided. Among men
18 having sex with men, the corresponding figures were 1708 (1294-2055) for ano-genital warts
19 and between 2.0 [0.23-4.5] and 2.5 [0.29-5.6] for anal cancer. Among 11- to 14-year-old
20 boys, 0.86 (0.15-2.4) Guillain-Barre syndrome cases would be induced annually.

21 **Interpretation:** A long-term program of HPV vaccination among boys in France would avoid
22 substantially more cancer cases than hypothetically induce Guillain-Barre syndrome cases, in
23 the general and specifically the homosexual population. Additional benefits may arise with
24 the possible vaccine protection against oro-laryngeal and –pharyngeal cancer.

Abbreviations: HPV: Human papillomavirus; MSM: Men who have sex with men; GBS: Guillain Barre syndrome; AGW: anogenital warts; AC: anal cancer; UI: uncertainty interval; CI: confidence interval

25 **Keywords**

26 HPV vaccine; Guillain-Barre Syndrome; Ano-genital warts; Anal cancer; Men who
27 have sex with men; Benefit-risk assessment; Monte Carlo method

28

29 **Introduction**

30 Human papillomavirus (HPV) infection is a common sexually transmitted infection, with over 80% of
31 sexually active individuals being infected at least once during their lifetime [1]. The majority of HPV
32 infections are often asymptomatic, transient and resolve spontaneously within a few years. However,
33 some infections may persist and lead to cancers. The multitude of HPV genotypes can be grouped
34 according to their high or low oncogenic potential. While HPV-16 and HPV-18 are mainly responsible
35 for cancers and precancerous lesions, HPV-6 and HPV-11 are responsible for non-malignant diseases
36 such as anogenital warts (AGWs).

37 The HPV-related burden of cervical and anal cancer (AC) is high among women, but a substantial
38 burden due to AC, oro-laryngeal and oro-pharyngeal cancer also exists among men [2,3]. This
39 evidence, has led to a global increase in gender-neutral HPV vaccination policies, which could be a
40 way to achieve the objective to reduce HPV transmission within populations and to eliminate cervical
41 cancer [4]. In France, the previous recommendation for Gardasil 9[®] targeting 11- to 14-year-old girls
42 (reimbursement possible up to age 19) is extended to boys from 2021 on [5].

43 HPV vaccines have been found to be safe during clinical phase and post-marketing studies, which did
44 not confirm suspicions of adverse events such as auto-immune disease, postural orthostatic
45 tachycardia syndrome or complex regional pain syndrome. However, in 2017, an analysis of the
46 French reimbursement and hospital discharge data using a self-controlled case series approach
47 found that HPV vaccination was associated with a 2.39 fold increased incidence of hospitalization for

48 Guillain-Barré Syndrome (GBS) during the 6 months following vaccination, among 13- to 16-year-old
49 girls (recommended target age at that time) [6]. However, the relation between HPV vaccine and GBS
50 was not confirmed in similar analyses in UK, Canada (Ontario and Quebec) and US [7–10] and only a
51 non-significant signal was reported from Finland [11]. GBS is thus a scientifically not confirmed
52 adverse event. In France, awaiting new evidence, authorities insist on the favorable benefit-risk ratio
53 of HPV vaccination for girls. Given the introduction of a gender-neutral policy, we aimed in the
54 present analysis at quantifying the benefits and hypothetical risks related to HPV vaccination that
55 would occur by 2070 among the male population (general male and MSM populations) in the context
56 of a long-term vaccination program.

57 In absence of clinical data on vaccine efficacy against oro-pharyngeal and penile cancers, we focused
58 on AGWs and ACs. This choice led to two different age windows to assess the benefit of vaccination,
59 defined as to cover the length of vaccine induced immunization and the length of the disease to
60 develop, leading to a mid-term assessment for AGW and long-term assessment for AC.

61 **Methods**

62 **Study design and data sources**

63 The general purpose of this work was to quantify benefits and risks of HPV vaccination with a
64 simulation study. The formulas of benefits and risks included fixed parameters and sampled
65 parameters. According to the Monte Carlo principle, the latter were randomly and independently
66 sampled from specified probability distributions. For parameterization, we aimed at including French
67 data wherever available or approached the situation in France with transposable data from other
68 European or high-income countries. As outputs, the model provided simultaneous estimates of the
69 annual number of cases avoided (benefits) and induced (risks) for a given population. Point estimates
70 are given as the median values and 95% uncertainty intervals (UI) as the 2.5% and 97.5% percentiles
71 of the distributions resulting from the 20,000 iterations. The model was written in SAS language and
72 we used SAS 9.4 version to run the simulations.

73 **General settings for benefit and risk modelling**

74 Population forecasts in 2070 were downloaded from the Insee (the French official statistics
75 authority) website, where we chose the central scenario for birth rate, life expectancy of newborns
76 and annual net migration [12]. To obtain the corresponding MSM group sizes, we applied the
77 proportions obtained in the 2016 French survey on global sexual health, namely 4.67% for men aged
78 15 to 35 years old, and 4.28% for men aged 15 to 65 years old [13]. Similar to 2018 HPV vaccine
79 coverage estimates for French girls [14], all our analyses assumed a 30% coverage among boys, with
80 80% receiving a full 2-dose series. We also made the arbitrary assumption that 10%, 40%, 40% and
81 10%, respectively of vaccine initiations occurred at age 11, 12, 13 or 14 years.

82 The maximal levels of vaccine efficacy achieved after immunization were considered as sampled
83 parameters, assuming identical efficacy in the general and the MSM population. Because vaccine
84 efficacies reported in the literature are based on small number of cases [15,16], we computed
85 confidence intervals using the Clopper-Pearson method [17]. The sampling procedure we developed
86 to simulate efficacy values was directly derived from this approach (S1 Methods). The duration of
87 induced immunity due to vaccine efficacy was chosen as at least 20 years at initial level [18]. As a result,
88 the protection against AGW was assessed among men aged 15 to 35 years old. Because of the latency
89 period between infection and cancer occurrence (ie, 10 to 20 years), the protection against AC was
90 assessed among men aged 25 to 65 years old. Finally, we made the following assumptions regarding
91 persistence of efficacy over years, whatever the considered event (AGW, AC) and population (general,
92 MSM): (i) maintained at its initial and maximal level during either 20 years after vaccination for fully
93 vaccinated men - or 10 years after vaccination for partially vaccinated men -, (ii) linear decline during
94 the following 10 years and (iii) no efficacy afterwards. An overview of all values for fixed parameters
95 and distribution choices for sampled ones can be found in S1 Table and S2 Table.

96 **Benefit modelling for anogenital warts**

97 This benefit depended on the proportion of AGW cases caused by HPV (δ_{AGW} , fixed), vaccine
98 coverage (VC , fixed), distribution of age at vaccination among the 4-year possible period ($v(11)$ to
99 $v(14)$, fixed), baseline incidence of AGW (I_{AGW} , sampled) and initial efficacy against incident AGW
100 ($E_{AGW}(0)$, sampled). Details can be found in S2 Methods, equation 2a. We used the AGW incidence as
101 estimated for 20- to 30-year-old men in France [19], ie 528 per 100,000 person years and applied a
102 correction factor to obtain I_{AGW} estimates (expressed as an incidence per 100,000 person years) for
103 the age range 15 to 35 years. This factor, 520/528, is based on the relative size of the two age groups
104 [19]. Thus, I_{AGW} was sampled from a Gamma distribution with the same 2.5% and 97.5% percentiles
105 95%-CI (487 – 568) and then multiplied by the correction factor. We obtained vaccine efficacy against
106 AGW due to HPV genotypes 6/11/16/18, $E_{AGW}(0)$, from a multicentric clinical trial among
107 heterosexual and homosexual men (89.9% (67.3% - 98.0%)) [15]. Values of $E_{AGW}(0)$ were simulated
108 as described in S1 Methods.

109 To estimate benefits in the MSM subgroup, we defined baseline incidence (denoted as I_{AGW}^{MSM}) by
110 sampling from the same distribution as I_{AGW} and we applied a multiplicative factor of 9/2.06 based
111 on the ratio of incidences estimated in Australia [20,21] among MSM and among the general male
112 population. Details can be found in S2 Methods, equation 2b.

113 **Benefits modelling for anal cancers**

114 As for the benefit against AGW, the benefit against AC depended on vaccine coverage and the age
115 distribution of boys among the 4-year possible period (VC , $v(11)$ to $v(14)$, fixed). It also depended
116 on the proportion of AC cases caused by HPV (δ_{AK} , fixed), on the baseline incidence of AC (I_{AC} ,
117 sampled) and on the initial efficacy against AC ($E_{AK}(0)$, sampled). Details can be found in S2 Methods,
118 equation 2c. To obtain AC incidence I_{AC} , we used 2019 data from the French Network of cancer
119 registries. Starting with the 214 cases observed in 2018 among 25- to 65-year-old men (Registries
120 report, Table 2, p 109) and to obtain the most plausible range of values for 2020, we applied the
121 upper and lower confidence limits of the annual progression rate estimate presented for 2019 (3.3%

122 (95%CI (1.5%-5.1%) [22]. I_{AC} (expressed as an incidence per 100,000 person-years) was sampled from
123 the Gamma distribution with 1.24 and 1.33 as 2.5% and 97.5% percentiles, respectively. We
124 estimated vaccine effectiveness against AC, $E_{AC}(0)$, based on the efficacy against incident ano-genital
125 infection with HPV genotypes 16/18 and probability of resulting AC. Efficacy was used as reported
126 from per-protocol analyses against HPV genotypes 16/18 in a multi-center clinical trial [16] among
127 MSM (84.5% (63.1%-94.6%)). Anal cancer can be caused by HPV types other than 16 and 18, while
128 the vaccine efficacy against infections by these other genotypes has not been reported in the
129 literature. Because 78.26% of AC cases are estimated to be due to genotypes 16/18 [23] but efficacy
130 against infections caused by genotypes other than 16/18 is not established, we assumed, in two best
131 and worst case scenarios that this efficacy was identical (best case) and null (worst case). In both
132 scenarios, values of $E_{AC}(0)$ were simulated according to the procedure detailed in S1 Methods.
133 Finally, we assumed that the delay between infection and cancer could range from 10 to 20 years,
134 with equal probability for various values of lag. Finally, as an extremely conservative scenario, we
135 also calculated the benefits using the efficacy reported from intention-to-treat analyses in the same
136 clinical trial, which is 46.5% (24.0%–62.7%)[16].

137 To obtain the baseline incidence among the MSM subgroup (now denoted as I_{AK}^{MSM}), we used
138 incidence data presented in a metaanalysis on HIV-negative MSM [24]. I_{AK}^{MSM} (expressed as an
139 incidence per 100,000 person-years) was sampled from the normal distribution with 1.63 and 8.67 as
140 2.5% and 97.5% percentiles, respectively, with truncation to positive values. Details can be found in
141 S2 Methods, equation 2d).

142 **Guillain-Barre Syndrome risk modelling**

143 The hypothetical additional risk of GBS among vaccinated boys depended on vaccine coverage (VC ,
144 fixed), baseline incidence of GBS (I_{GBS} , sampled) and relative risk of GBS induced by vaccination (RR ,
145 sampled). Details can be found in S3 Methods). We obtained I_{GBS} , from the general equation for the
146 male age-specific rates in Western countries as reported in a meta-analysis, which we applied to boys

147 aged 13 years [25]. We obtained the uncertainty around this value by assuming a similar precision as
148 the one reported for the 10- to 19-year-old boys. Thus, I_{GBS} was sampled from the Gamma
149 distribution with 0.70 and 1.26 as 2.5% and 97.5% percentiles, respectively. From the French analysis
150 reporting an increased risk of GBS after vaccination, we chose the relative risk estimated with a self-
151 controlled case series approach during a 6-month risk period (2.39 (1.21-4.72)) [6]. Thus, RR after
152 each vaccine administration was sampled from the Lognormal distribution with 1.21 and 4.72 as 2.5%
153 and 97.5% percentiles, respectively.

154 **Results**

155 The population forecasts for 2070 were of 8.72M 15- to 35-year-old men and 17.4M 25- to 65-year-
156 old men, representing an increase of 6.1% and 4.2%, respectively, compared to the 2020 population.
157 Based on 2070 demographic projections, about 418,000 boys will become eligible to vaccination each
158 year. This means that about 225,000 vaccine doses would be necessary each year to achieve the
159 assumed 30% coverage with 80% of full 2-dose series.

160 We estimated that during 2070, a first episode of AGW would be averted for 9310 (95%UI, 7050 to
161 11200) men aged 15-35 years old in the general French population (Table 1, Figure 1). In the best-
162 case scenario for AC, 19.2 (95%-UI, 15.0-22.6) cases would be averted among men aged 25-65 years,
163 compared to 15.1 (95%-UI, 11.7-17.7) in the worst-case scenario. We estimated that 0.82 (95%-UI,
164 0.15-2.30) GBS cases would be hypothetically induced by HPV vaccination during 2070, i.e., one
165 additional case every 1.2 years (95%-UI, 0.42-6.2 years) (Table 1). Specifically, among the MSM
166 population, we estimated that during 2070, about 1910 AGW (95%-UI, 1440-2290) would be averted
167 among men aged 15-35 years (Table 1, Figure 1). In the best-case scenario for AC, 2.6 (95%-UI, 0.29-
168 5.7) cases would be averted among MSM aged 25-65 years, compared to 2.0 (95%UI, 0.23-4.5) in the
169 worst-case scenario.

170

171 **Table 1: Benefit (avoided cases) and risks (induced cases) of HPV vaccination in the French**
 172 **male population during 2070.**

Population type	Impact type	Outcome	Evaluated age range (years)	Annual number avoided or induced, in the evaluated age range median (95%-UI)
General	Benefit	Anogenital warts	15-35	9310 (7050 – 11,200)
		Anal cancer	25-65	Best: 19.2 (15.0 – 22.6) Worst: 15.1 (11.7 – 17.7)
MSM ^a	Benefit	Anogenital warts	15-35	1907 (1444 - 2291)
		Anal cancer	25-65	Best: 2.6 (0.29 – 5.7) Worst: 2.0 (0.23 – 4.5)
General	Risk	Guillain Barre Syndrome	11-14	0.82 (0.15 -2.3)

173 ^a MSM population represents a subgroup (around 4%) of the general male adult population.

174

175 Finally, if vaccine efficacy only reached the intention-to-treat estimate (relevant if a fraction of boys
 176 were already infected at vaccination), then the annual number of avoided AC would decreased to 8.5
 177 (95%-UI, 4.5-11.7) in the general population and 1.1 (95%-UI, 0.12-2.7) in the MSM population.

178 Results obtained under other choices of coverage could easily be deduced from those of the present
 179 analysis (with 30% CV), because both benefits and risks are proportionally dependent on this
 180 parameter, as it is shown in Appendix (Methods S2 and S3).

181 Discussion

182 In this modeling study on HPV vaccination among the male population in France, we estimated that
 183 under the condition of a stable vaccination program with 30% coverage overtime, at least 15 and up

184 to 19 anal cancer cases would be avoided each year among 25- to 65-year-old men and more than
185 9000 men aged 15-35 years would not experience their first episode of ano-genital warts. In the
186 same vaccination program, 0.82 cases of GBS could hypothetically be induced among 11- to 14-year-
187 old boys annually. In terms of benefit-risk ratio, for each vaccine-induced case of GBS, between 18.1
188 to 23.4 cases of anal cancer (depending on scenarios) would be avoided. Based on the results of our
189 relatively conservative analysis, the claim is valid that HPV vaccination has more individual benefits
190 than risks not only for girls, but for boys as well, even when assuming that HPV vaccine was
191 associated with an increased risk in GBS, which is a scientifically not confirmed hypothesis. In our
192 analysis, this was observed even if using intention-to-treat efficacy of HPV vaccination against anal
193 cancer, assuming that a certain fraction of boys would be HPV infected at time of vaccination. This
194 could be the case given the French recommendation for catch-up vaccination up to age 19 years.

195 We included in our analyses the two types of vaccine-preventable diseases for which the clinical
196 efficacy of HPV vaccine is documented, both however presenting limitations: as anal cancer has a low
197 incidence among men (about 1 per 100,000), the expected risk reduction is relatively low. Ano-
198 genital warts have high incidence among men, but their severity cannot be compared neither to a
199 severe neurological condition such as GBS, nor to cancer. Therefore, we acknowledge that this first
200 evaluation of vaccination impact is of limited scope, while it provides a methodological framework
201 for future wider analyses on HPV vaccine benefits. HPV vaccines are expected to prevent oro-
202 laryngeal and -pharyngeal cancer, which are much more frequent (about 500 per 100,000) and for
203 which an increasing fraction is not associated to tobacco and alcohol consumption, but to HPV
204 infection [26]. Evidence on clinical vaccine efficacy against these other types of cancer is expected to
205 emerge [27,28], and our analysis will need to be expanded accordingly.

206 We conducted a specific analysis for the MSM population, for whom quality data on disease risk
207 were available. The observed absolute benefit was low compared to the general population, as MSM
208 represented only a small part (about 4%) of the general male population, but the results correspond

209 to a high risk reduction when expressed as averted cases per 100,000. The ratio of benefits and risks
210 associated with HPV vaccination would be between 55 and 70 for this subgroup. HPV vaccine
211 recommendations for men targeted until 2020 only MSM up to age 26. Impact of this policy was
212 limited by low uptake, amongst others due to fear of stigmatization and the fact that vaccination has
213 lower efficacy after established infection, as evidenced in clinical trials [16]. Expanding the
214 recommendation to adolescent boys will help improve this situation. In addition, the annual number
215 of cases averted in the non-MSM population (calculated as the difference between the benefit in the
216 general population and the benefit in the MSM sub-population), namely 7439 for AGW, 13 to 16 for
217 AC, support the decision to make prevention from HPV disease accessible to all men.

218 Benefit-risk balance assessment for vaccination against cancer is challenging, as it requires modelling
219 preventative effects that occur in a long-term timeframe of 20 years and more, while adverse events
220 following vaccination would occur within a few weeks or months. Other possible approaches could
221 have been cohort or dynamic modeling, the latter requiring hypotheses on sexual contact networks.
222 Such models have been developed to assess the impact of HPV vaccination on genital warts
223 incidence [29]. They are also frequently used in a cost-effectiveness perspective, as recently done in
224 France [30] or globally [31–35]

225 For the present analysis, we have opted for a simpler approach, applying known current values of
226 vaccine efficacy and disease-induced risk on a future hypothetical population. We needed to assume
227 population stability in terms of vaccination coverage, population size in age groups and disease risk.
228 This approach puts the emphasis on total number of avoided and hypothetically caused cases, and
229 not on individual average risks. Further limitations are that some input parameters such as
230 hypothetical GBS risk increase by vaccination or proportion of vaccinees receiving the full schedule
231 were extrapolated from girls, while others, such as baseline incidence of AGWs and GBS, were
232 derived from data in other countries. Future studies estimating these parameters in French men
233 would be helpful to make benefit estimations more specific for the French male population.

234 Another limitation of our approach is that we do not include indirect protection effects, which are
235 important for the public health perspective. HPV vaccines protect against acquisition of infection,
236 and therefore strongly impact transmission dynamics in the population. However, more complex
237 models accounting for herd immunity would be required in the absence of solid population-level
238 estimates of indirect effectiveness [36]. For HPV vaccination, the full public health perspective would
239 also require modeling prevention among women. In effect, the prevalence of HPV infection is high in
240 women and in addition to AGW, HPVs are responsible for almost all cervical cancers, for many
241 anogenital cancers and, to a lesser extent, for oropharyngeal cancers[37]. Thus, one important
242 population benefit from HPV vaccination for boys in France will be the reduction of viral transmission
243 to women, in particular given the relatively low coverage of 30% among girls [38] . Our present
244 analysis thus does not present a larger public health perspective, but focusses on the male
245 population's isolated benefit from vaccination. Finally, this analysis can inform decision making by
246 health care providers and public health professionals and provide quantitative elements for
247 communication on HPV vaccination for adolescent boys.

248 **Declaration of Competing Interest**

249 The authors declare that they have no known competing financial interests or personal relationships
250 that could have appeared to influence the work reported in this paper.

251 **Acknowledgments**

252 The authors wish to thank A.S. Barret and D. Levy-Bruhl (Santé Publique France) for fruitful discussion
253 on HPV vaccination. They also wish to thank Y. Mikaellof (Assistance Publique-Hôpitaux de Paris,
254 Hôpital Bicêtre, Unité de Rééducation Neurologique Infantile) for fruitful discussion on Guillain Barre
255 Syndrome.

256

257 **Figure caption**

258 Fig 1: Annual number of first episodes of anogenital warts (left graph) and anal cancers (right
259 graph) avoided among French men during 2070, given an HPV vaccination program targeting
260 boys.

261 **Supplementary material**

262 S1 Methods. Procedure for vaccine efficacy simulations

263 S2 Methods. Benefit formulas

264 S3 Methods. Risk formula

265 S1 Table: Overview of sampled parameters

266 S2 Table: Overview of fixed parameters

267

268

269

270

271 **References**

- 272 [1] Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring
273 human papillomavirus in the United States. *Sex Transm Dis* 2014;41:660–4.
274 <https://doi.org/10.1097/OLQ.000000000000193>.
- 275 [2] Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjosé S. Estimation of the overall
276 burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV
277 vaccine types in women and men in Europe. *Infect Agent Cancer* 2017;12:19.
278 <https://doi.org/10.1186/s13027-017-0129-6>.
- 279 [3] Shield KD, Marant Micallef C, de Martel C, Heard I, Megraud F, Plummer M, et al. New cancer
280 cases in France in 2015 attributable to infectious agents: a systematic review and meta-
281 analysis. *Eur J Epidemiol* 2018;33:263–74. <https://doi.org/10.1007/s10654-017-0334-z>.
- 282 [4] Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination
283 and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78
284 low-income and lower-middle-income countries. *Lancet (London, England)* 2020;395:575–90.
285 [https://doi.org/10.1016/S0140-6736\(20\)30068-4](https://doi.org/10.1016/S0140-6736(20)30068-4).
- 286 [5] Overview of vaccination guidelines. Papillomavirus vaccination in boys n.d. [https://www.has-](https://www.has-sante.fr/upload/docs/application/pdf/2020-05/overview_of_vaccination_guidelines_papillomavirus_vaccination_in_boys.pdf)
287 [sante.fr/upload/docs/application/pdf/2020-](https://www.has-sante.fr/upload/docs/application/pdf/2020-05/overview_of_vaccination_guidelines_papillomavirus_vaccination_in_boys.pdf)
288 [05/overview_of_vaccination_guidelines_papillomavirus_vaccination_in_boys.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2020-05/overview_of_vaccination_guidelines_papillomavirus_vaccination_in_boys.pdf) (accessed
289 February 4, 2021).
- 290 [6] Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus
291 vaccination and risk of autoimmune diseases: A large cohort study of over 2million young girls
292 in France. *Vaccine* 2017;35:4761–8. <https://doi.org/10.1016/j.vaccine.2017.06.030>.
- 293 [7] Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human
294 papilloma virus vaccine: A self-controlled case-series study in England. *Vaccine* 2017;35:1729–

- 295 32. <https://doi.org/10.1016/j.vaccine.2017.01.076>.
- 296 [8] Liu EY, Smith LM, Ellis AK, Whitaker H, Law B, Kwong JC, et al. Quadrivalent human
297 papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8
298 HPV Vaccine Cohort Study. *CMAJ* 2018;190:E648–55. <https://doi.org/10.1503/cmaj.170871>.
- 299 [9] Deceuninck G, Sauvageau C, Gilca V, Boulianne N, De Serres G. Absence of association
300 between Guillain-Barré syndrome hospitalizations and HPV-vaccine. *Expert Rev Vaccines*
301 2018;17:99–102. <https://doi.org/10.1080/14760584.2018.1388168>.
- 302 [10] Gee J, Sukumaran L, Weintraub E, Vaccine Safety Datalink Team. Risk of Guillain-Barré
303 Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety
304 Datalink. *Vaccine* 2017;35:5756–8. <https://doi.org/10.1016/j.vaccine.2017.09.009>.
- 305 [11] Skufca J, Ollgren J, Artama M, Ruokokoski E, Nohynek H, Palmu AA. The association of adverse
306 events with bivalent human papilloma virus vaccination: A nationwide register-based cohort
307 study in Finland. *Vaccine* 2018;36:5926–33. <https://doi.org/10.1016/j.vaccine.2018.06.074>.
- 308 [12] Age pyramid: population projections 2070. Insee n.d.
309 <https://www.insee.fr/en/statistiques/2524488> (accessed December 15, 2020).
- 310 [13] Bajos N, Rahib D, Lydié N. Baromètre santé 2016. Genre et sexualité 2018.
311 [https://www.santepubliquefrance.fr/determinants-de-sante/sante-](https://www.santepubliquefrance.fr/determinants-de-sante/sante-sexuelle/documents/enquetes-etudes/barometre-sante-2016.-genre-et-sexualite)
312 [sexuelle/documents/enquetes-etudes/barometre-sante-2016.-genre-et-sexualite](https://www.santepubliquefrance.fr/determinants-de-sante/sante-sexuelle/documents/enquetes-etudes/barometre-sante-2016.-genre-et-sexualite) (accessed
313 December 15, 2020).
- 314 [14] Fonteneau L, Barret A, Lévy-Bruhl D. Évolution de la couverture vaccinale du vaccin contre le
315 papillomavirus en France – 2008-2018. *Bull Epidémiol Hebd* 2019;22–23:424–30.
- 316 [15] Goldstone SE, Jessen H, Palefsky JM, Giuliano AR, Moreira ED, Vardas E, et al. Quadrivalent
317 HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males.
318 *Vaccine* 2013;31:3849–55. <https://doi.org/10.1016/j.vaccine.2013.06.057>.

- 319 [16] Palefsky JM, Giuliano AR, Goldstone S, Moreira ED, Aranda C, Jessen H, et al. HPV vaccine
320 against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011;365:1576–85.
321 <https://doi.org/10.1056/NEJMoa1010971>.
- 322 [17] CLOPPER CJ, PEARSON ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of
323 the Binomial. *Biometrika* 1934;26:404–13.
- 324 [18] Schwarz TF, Huang L-M, Valencia A, Panzer F, Chiu C-H, Decreux A, et al. A ten-year study of
325 immunogenicity and safety of the AS04-HPV-16/18 vaccine in adolescent girls aged 10-14
326 years. *Hum Vaccin Immunother* 2019;15:1970–9.
327 <https://doi.org/10.1080/21645515.2019.1625644>.
- 328 [19] Aubin F, Aynaud O, Judlin P, Carcopino X, Jacquard A, Okaïs C, et al. Incidence des condylomes
329 chez les femmes et les hommes 2011:A74–5. [https://www.em-](https://www.em-consulte.com/en/article/674552)
330 [consulte.com/en/article/674552](https://www.em-consulte.com/en/article/674552) (accessed December 15, 2020).
- 331 [20] Pirotta M, Stein AN, Conway EL, Harrison C, Britt H, Garland S. Genital warts incidence and
332 healthcare resource utilisation in Australia. *Sex Transm Infect* 2010;86:181–6.
333 <https://doi.org/10.1136/sti.2009.040188>.
- 334 [21] Jin F, Prestage GP, Kippax SC, Pell CM, Donovan B, Templeton DJ, et al. Risk factors for genital
335 and anal warts in a prospective cohort of HIV-negative homosexual men: the HIM study. *Sex*
336 *Transm Dis* 2007;34:488–93. <https://doi.org/10.1097/01.olq.0000245960.52668.e5>.
- 337 [22] Defossez G, Le Guyader-Peyrou S, Uhry Z, Grosclaude P, Colonna M, Dantony E, et al.
338 Estimations nationales de l’incidence et de la mortalité par cancer en France métropolitaine
339 entre 1990 et 2018 - Volume 1 : Tumeurs solides : Étude à partir des registres des cancers du
340 réseau Francim 2019. [https://www.santepubliquefrance.fr/maladies-et-](https://www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-sein/documents/rapport-synthese/estimations-nationales-de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-)
341 [traumatismes/cancers/cancer-du-sein/documents/rapport-synthese/estimations-nationales-](https://www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-sein/documents/rapport-synthese/estimations-nationales-de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-)
342 [de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-](https://www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-sein/documents/rapport-synthese/estimations-nationales-de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-)

343 volume-1-tumeurs-solides-etud.

344 [23] Abramowitz L, Jacquard A-C, Jaroud F, Haesebaert J, Siproudhis L, Pradat P, et al. Human
345 papillomavirus genotype distribution in anal cancer in France: the EDiTH V study. *Int J Cancer*
346 2011;129:433–9. <https://doi.org/10.1002/ijc.25671>.

347 [24] Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human
348 papillomavirus infection and associated neoplastic lesions in men who have sex with men: a
349 systematic review and meta-analysis. *Lancet Oncol* 2012;13:487–500.
350 [https://doi.org/10.1016/S1470-2045\(12\)70080-3](https://doi.org/10.1016/S1470-2045(12)70080-3).

351 [25] Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré
352 syndrome: a systematic review and meta-analysis. *Neuroepidemiology* 2011;36:123–33.
353 <https://doi.org/10.1159/000324710>.

354 [26] Timbang MR, Sim MW, Bewley AF, Farwell DG, Mantravadi A, Moore MG. HPV-related
355 oropharyngeal cancer: a review on burden of the disease and opportunities for prevention
356 and early detection. *Hum Vaccin Immunother* 2019;15:1920–8.
357 <https://doi.org/10.1080/21645515.2019.1600985>.

358 [27] Villa A, Patton LL, Giuliano AR, Estrich CG, Pahlke SC, O'Brien KK, et al. Summary of the
359 evidence on the safety, efficacy, and effectiveness of human papillomavirus vaccines:
360 Umbrella review of systematic reviews. *J Am Dent Assoc* 2020;151:245-254.e24.
361 <https://doi.org/10.1016/j.adaj.2019.10.010>.

362 [28] Lehtinen T, Elfström KM, Mäkitie A, Nygård M, Vänskä S, Pawlita M, et al. Elimination of HPV-
363 associated oropharyngeal cancers in Nordic countries. *Prev Med (Baltim)* 2021;144:106445.
364 <https://doi.org/10.1016/j.ypmed.2021.106445>.

365 [29] Korostil IA, Ali H, Guy RJ, Donovan B, Law MG, Regan DG. Near elimination of genital warts in
366 Australia predicted with extension of human papillomavirus vaccination to males. *Sex Transm*

- 367 Dis 2013;40:833–5. <https://doi.org/10.1097/OLQ.0000000000000030>.
- 368 [30] Majed L, Bresse X, El Mouaddin N, Schmidt A, Daniels VJ, Pavelyev A, et al. Public health
369 impact and cost-effectiveness of a nine-valent gender-neutral HPV vaccination program in
370 France. *Vaccine* 2021;39:438–46. <https://doi.org/10.1016/j.vaccine.2020.10.089>.
- 371 [31] Brisson M, Bénard É, Drolet M, Bogaards JA, Baussano I, Vänskä S, et al. Population-level
372 impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic
373 review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public
374 Heal* 2016;1:e8–17. [https://doi.org/10.1016/S2468-2667\(16\)30001-9](https://doi.org/10.1016/S2468-2667(16)30001-9).
- 375 [32] Díez-Domingo J, Sánchez-Alonso V, Villanueva R-J, Acedo L, Tuells J. Impact of a Gender-
376 Neutral HPV Vaccination Program in Men Who Have Sex with Men (MSM). *Int J Environ Res
377 Public Health* 2021;18. <https://doi.org/10.3390/ijerph18030963>.
- 378 [33] Drolet M, Bénard É, Pérez N, Brisson M, HPV Vaccination Impact Study Group. Population-
379 level impact and herd effects following the introduction of human papillomavirus vaccination
380 programmes: updated systematic review and meta-analysis. *Lancet (London, England)*
381 2019;394:497–509. [https://doi.org/10.1016/S0140-6736\(19\)30298-3](https://doi.org/10.1016/S0140-6736(19)30298-3).
- 382 [34] Qendri V, Bogaards JA, Baussano I, Lazzarato F, Vänskä S, Berkhof J. The cost-effectiveness
383 profile of sex-neutral HPV immunisation in European tender-based settings: a model-based
384 assessment. *Lancet Public Heal* 2020;5:e592–603. [https://doi.org/10.1016/S2468-
385 2667\(20\)30209-7](https://doi.org/10.1016/S2468-2667(20)30209-7).
- 386 [35] Kim JJ, Simms KT, Killen J, Smith MA, Burger EA, Sy S, et al. Human papillomavirus vaccination
387 for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. *PLoS Med*
388 2021;18:e1003534. <https://doi.org/10.1371/journal.pmed.1003534>.
- 389 [36] Brisson M, van de Velde N, Franco EL, Drolet M, Boily M-C. Incremental impact of adding boys
390 to current human papillomavirus vaccination programs: role of herd immunity. *J Infect Dis*

391 2011;204:372–6. <https://doi.org/10.1093/infdis/jir285>.

392 [37] Serrano B, Brotons M, Bosch FX, Bruni L. Epidemiology and burden of HPV-related disease.

393 Best Pract Res Clin Obstet Gynaecol 2018;47:14–26.

394 <https://doi.org/10.1016/j.bpobgyn.2017.08.006>.

395 [38] Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost-effectiveness of

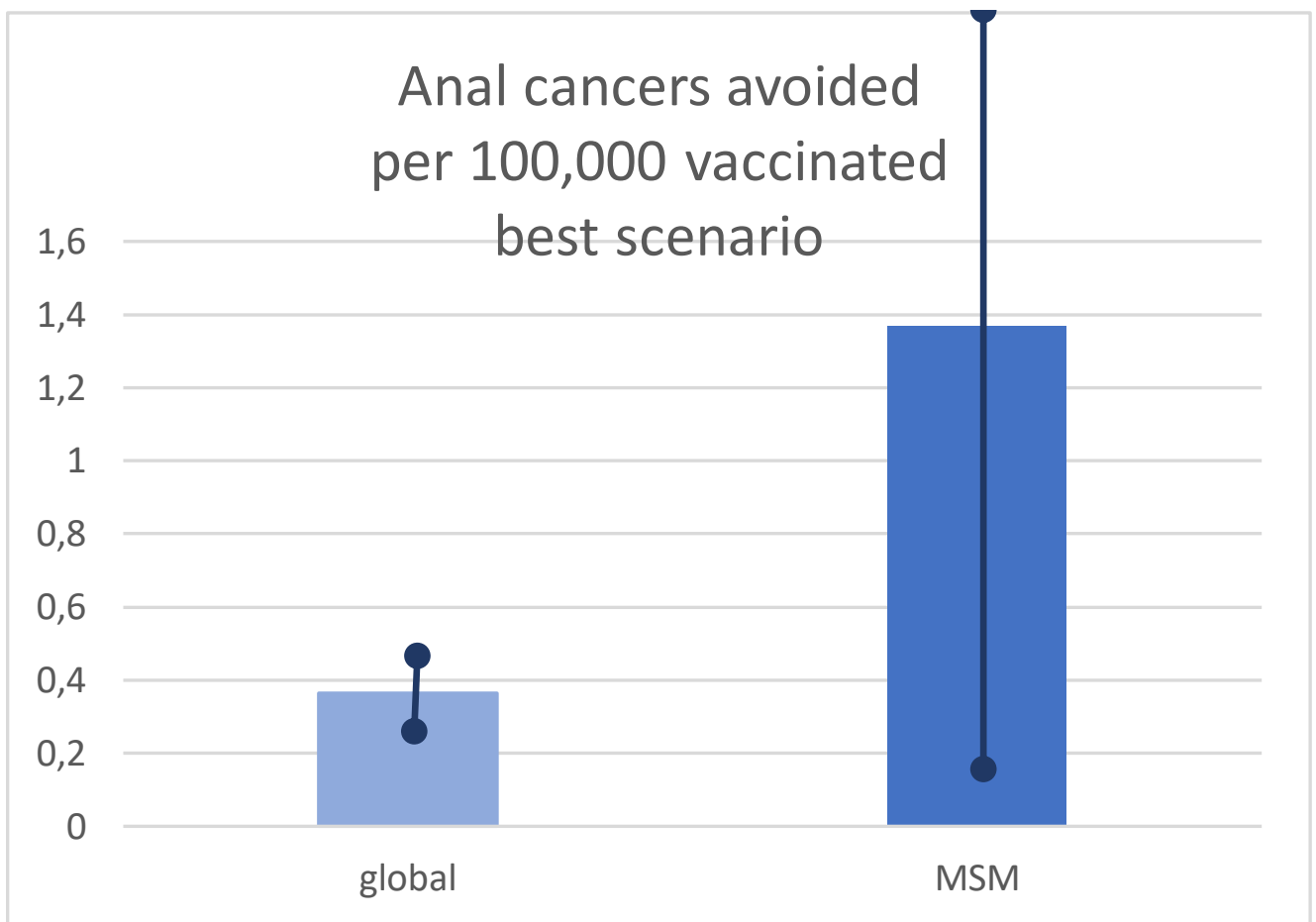
396 male HPV vaccination in the United States. Vaccine 2011;29:8443–50.

397 <https://doi.org/10.1016/j.vaccine.2011.07.096>.

398

399

Anal cancers avoided
per 100,000 vaccinated
best scenario



Anogenital warts avoided per 100,000 vaccinated

