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Title

Human Papillomavirus vaccination coverage, policies, and practical implementation across Europe

Authors

Ngoc-Ha Nguyen-Huu¹, Nathalie Thilly^{1, 2}, Tarik Derrough³, Emmanouela Sdona³, Frédérique Claudot¹,
Céline Pulcini^{1, 4}, Nelly Agrinier^{1, 5}, HPV Policy working group⁶

Affiliations

¹ Université de Lorraine, Apemac, F-54000 Nancy, France,

² CHRU Nancy, Université de Lorraine, Plateforme d'Aide à la Recherche Clinique, F-54000 Nancy,
France

³ European Centre for Disease Prevention and Control, Sweden

⁴ Université de Lorraine, CHRU-Nancy, Infectious Diseases Department, F-54000 Nancy, France

⁵ CHRU-Nancy, INSERM, Université de Lorraine, CIC, Epidémiologie Clinique, F-54000 Nancy, France

⁶ The members of the working group are listed at the end of the article

Corresponding Author

Nelly Agrinier

Inserm, CHRU Nancy, Université de Lorraine, CIC-1433 Epidémiologie clinique

Hôpitaux de Brabois

Allée du Morvan

54500 Vandoeuvre-lès-Nancy

France

Phone: +33 3 83 85 21 64

Fax: +33 3 83 85 12 05

Email: n.agrinier@chru-nancy.fr

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1 **Introduction**

2 Over the last decade, Human Papillomavirus (HPV) vaccination has been effective in the prevention of
3 HPV related diseases [1–4].

4 A decrease of HPV 6/11/16/18 infection, genital warts, low-grade cytological cervical abnormalities,
5 and histologically proven cervical abnormalities has been observed after HPV vaccine introduction.
6 [4,5] Moreover, results of randomised trials confirmed a high safety profile of HPV vaccines [6].
7 Maximal benefit is observed among girls vaccinated before HPV exposure in countries that have
8 achieved high vaccination coverage rates (VCR) [4,7].

9 However, HPV remains a significant source of morbidity and mortality worldwide, emphasizing the
10 need for vaccination programmes to reach high population coverage [5]. In May 2018, the World
11 Health Organisation (WHO) called for the elimination of cervical cancer as a public health problem,
12 and set a target of 90% coverage of HPV vaccination by 2030 in the Global Strategy Towards The
13 Elimination Of Cervical Cancer As A Public Health Problem drafted in 2019 [8]. In European countries,
14 HPV vaccination has been gradually introduced in the national immunisation programmes since 2007,
15 but policies and VCR vary across countries [9,10]. Despite the introduction of free of charge HPV
16 vaccine in the French immunisation schedule in 2007 [11], HPV VCR has been declining ever since in
17 France to reach 21% for two doses in 2017 [12]. Other European countries faced suboptimal HPV
18 VCR, such as Germany [13]. On the other hand, some countries, such as the United Kingdom [14],
19 have remarkably high HPV VCR. Nevertheless, to the best of our knowledge, no comprehensive
20 overview of HPV VCR is available for European countries since the VENICE2 report in 2010 [9] and the
21 review article by Poljak et al. focusing on Central and Eastern European countries in 2013 [10].
22 Factors linked to such wide variations in VCR between countries in Europe are not well explored in the
23 literature.

24 Our objectives were therefore to describe HPV VCR in the target population across Europe, as well as
25 to explore HPV vaccination policies and specific measures taken to facilitate the practical
26 implementation of the HPV programme in order to reach high uptake in the target population.

27 **Methods**

28 A review of national health authorities' websites and published studies was followed by a cross-
29 sectional survey (prefilled questionnaire) distributed to selected experts from each Member State, in
30 order to validate publicly available data and explore specific measures taken to facilitate the practical
31 implementation of the HPV programme in order to reach high uptake in the target population.

32 ***Review of national authorities' websites and of the literature***

33 Review of institutional websites and of the literature published on HPV VCR, policies and practical
34 implementation was conducted for Switzerland and the following 30 European Union/European
35 Economic Area (EU/EEA) countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic,
36 Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia,
37 Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia,
38 Slovenia, Spain, Sweden and the United Kingdom. Belgium was considered as two separate areas in
39 the results, as Flanders and Walloon-Brussels have different HPV vaccination policies, leading to a
40 total of 32 geographical areas investigated.

41 Health authorities' websites were reviewed (by NHH, double checked by NA) to identify eligible
42 reports for each country. 'HPV' and 'human papillomavirus' terms were translated in the corresponding
43 language and entered in the research tool available on each website. To confirm the target age for
44 vaccination, the European Centre for Disease Control (ECDC) vaccination schedule tool [15] was used.

45 Peer-reviewed articles published in PubMed from January, 1 2006 to January, 31 2017 and indexed in
46 Medline were also reviewed to identify studies aiming to describe HPV VCR (for 1-dose and full-course
47 immunisation), related policies and practical implementation. Languages were restricted to English
48 and French. Search terms included the following MeSH and usual terms: (((("Papillomavirus
49 Vaccines"[Mesh] OR "human papillomavirus vaccine, L1 type 16,18"[Supplementary Concept] OR
50 "human papillomavirus vaccine, TA"[Supplementary Concept] OR "papillomavirus vaccinated"[tw] OR
51 "papillomavirus vaccination"[tw] OR "papillomavirus vaccinations"[tw] OR "papillomavirus vaccine"[tw]
52 OR "papillomavirus vaccines"[tw] OR "papilloma virus vaccination"[tw] OR "papilloma virus
53 vaccinations"[tw] OR "papilloma virus vaccine"[tw] OR "papilloma virus vaccines"[tw] OR "hpv

54 vaccine"[tw] OR "hpv vaccines"[tw] OR "v503"[tw] OR "9v HPV"[tw] OR "9vHPV"[tw] OR "4vHPV"[tw]
55 OR "qhpv"[tw] OR "2Vhpv"[tw] OR "cervarix"[tw] OR "cervarix"[tw] OR "cervarix's"[tw] OR
56 "cervarixtm"[tw] OR "cervarixtrade"[tw] OR "Gardasil"[tw] OR "gardasil"[tw] OR "gardasil's"[tw] OR
57 "gardasil9"[tw] OR "gardasiltrade"[tw] OR "silgard"[tw]) AND "Vaccination/statistics and numerical
58 data"[Mesh]) OR "Papillomavirus Infections/prevention and control"[Mesh]) AND "<specific name of
59 country or Europe>").

60 NHHH screened the titles and abstracts of the scientific publications resulting from this search to
61 assess their eligibility and extracted the data from the selected full-text articles.

62 In November 2017, a standardised form (available upon request to the authors) was used to collect
63 information about HPV VCR, vaccination policies and practical implementation. Information on the
64 most recent VCR for 1-dose and full-course immunisation was collected only for females of the target
65 age in each country. Additionally, the source of the information, i.e. vaccination registries, health care
66 reimbursement files, reports from national surveys or scientific publications, was collected.
67 Information about vaccination policies focused on year of introduction of HPV vaccine in the national
68 immunisation programme, target gender and age (including age for catch-up), type of vaccine used
69 (bivalent, quadrivalent, or nonavalent), out-of-pocket cost, i.e. cost that are not covered by health
70 insurance if any, and regulatory aspects, i.e. parental consent required or not, type of consent
71 (written or oral) if any, and whether provision of information to the recipient is mandatory or not.
72 Information on vaccination practical implementation focused on mandatory medical prescription prior
73 to vaccine administration, vaccination settings, dispensing of the vaccine, and measures used to
74 remind the target population of the vaccination programme. The same information on vaccination
75 policies and practical implementation specific to males was also collected.

76

77 ***Cross-sectional survey***

78 Experts in public health or infection specialists in each country (one per country) were identified by
79 searching Pubmed using the name of the EU/EEA country and the terms related to HPV used in the
80 previous review, and contacted by e-mail by CP from November, 20 2017 to January, 22 2018. The

81 aforementioned pre-filled standardized forms were double checked, validated or completed by the
82 experts from November 2017 to April 2018. In case of data completion, the experts were asked to
83 provide the scientific publications or reports supporting the additional data. They were also asked to
84 review the final draft of the manuscript before submission.

85

86 ***Statistical analysis***

87 HPV VCR results are reported overall as percentages. Countries were classified into four categories
88 defined empirically according to their VCR level for at least 1-dose immunisation in females: high
89 (>70%), moderate (51-70%), low (31-50%) and very low (\leq 30%). Most recent data on VCR, and
90 when available, complete schedule VCR rates for the oldest age group was used for classification.

91 To identify vaccination policies and practical implementation steps associated with high HPV VCR in
92 females, geographical areas' characteristics regarding policies and practical implementation were then
93 described by their frequency stratified on their VCR category (in females).

94 As no published data on HPV VCR was available in males, vaccination policies and practical
95 implementation could not be described according to HPV VCR, and were thus described overall in
96 males.

97

98 **Results**

99 A total of 90 health authorities' websites and related webpages (Supplemental material Tables 1-6)
100 were browsed for HPV VCR, policies and practical implementation (Figure 1). Similarly, from 217
101 articles compiled from the PubMed search, a total of 32 (list of references and summary available in
102 Supplemental material Table 7) were included in the analysis (Figure 2). For the cross-sectional
103 survey, a total of 71 experts from 31 countries were contacted and 31 experts from 28 countries (all
104 except Bulgaria, Hungary, and Iceland) agreed to participate.

105

106 ***Description of HPV vaccination coverage rates***

107 HPV VCR estimates, target age and HPV vaccination settings were obtained in 25 (25/32)
108 geographical areas (Figure 3). HPV VCR was high in ten geographical areas (10/25) : Belgium
109 Flanders, Finland, Hungary, Iceland, Malta, Norway, Portugal, Spain, Sweden, and the United
110 Kingdom, moderate in seven areas (7/25): the Czech Republic, Denmark, Ireland, Italy, Luxembourg,
111 the Netherlands, and Switzerland, low in four areas (4/25): Belgium Walloon Brussels, Germany,
112 Latvia and Slovenia, and very low in four areas (4/25): Bulgaria, France, Greece, and Poland.

113

114 ***HPV vaccination policies***

115 Vaccination recommendations were usually set at a national level and policies varied widely across
116 Europe (Table 1). However, implementation was often done at regional level. Accordingly, subnational
117 differences in vaccination policy were observed in 8/32 areas. For example, subnational differences in
118 target gender (Saxony region's male vaccination in Germany), age (Belgium, Italy, Spain, the United
119 Kingdom), and out-of-pocket cost (Poland) were observed.

120

121 ***Year of introduction of HPV vaccination and respective programmes***

122 Of the 32 geographical areas considered, 31 had HPV vaccination recommended in their national
123 immunisation programme. The first areas which implemented HPV vaccination were France, Germany,
124 Italy, Spain, and the United Kingdom in 2007. The last one was Estonia, which started HPV
125 vaccination in 2018.

126 In areas with high VCR, year of introduction of vaccination varied from 2007 for Belgium-Flanders and
127 Spain to 2014 for Hungary. In areas with very low VCR, year of introduction of vaccination varied from
128 2007 for France to 2012 for Bulgaria. In Romania, the school vaccination programme implemented in
129 2008 had been discontinued after three attempts due to low acceptance [16].

130

131 *Target age and gender*

132 The target age for vaccination among females ranged from 9 to 15 years old. All areas with high VCR
133 set the target age between 10 and 13 years old for females, while all areas with very low VCR set it
134 between 11 and 15 years of age. Seven areas (7/32) recommended gender neutral vaccination, i.e.
135 vaccination in all males and females: three of these (3/7, i.e. the Czech Republic, Italy, and
136 Switzerland) in areas with moderate VCR, one (1/4, i.e. Poland) in areas with very-low VCR, and three
137 in areas with no VCR published, with a target age ranging from 9 to 26 years old.

138

139 *Catch-up vaccination programmes*

140 Two main types of catch-up programmes could be distinguished: extended catch-up with a defined
141 target age or mass catch-up during a limited period of time.

142 Five areas (Finland, Norway Portugal, Spain, and the United Kingdom) with high VCR (5/10) had
143 offered a mass catch-up during a limited period of time, i.e., at the time of implementation of the HPV
144 vaccination programme for Finland, Portugal, Spain, and the United Kingdom, and seven to nine years
145 after implementation in Norway. No such catch-up programme was observed in areas with very low
146 VCR (0/4).

147 Extended catch-up was less frequent in areas with high VCR (3/10), (i.e. Finland, Sweden, and the
148 United Kingdom) than in areas with low (4/4) or very low VCR (4/4).

149

150 *Type of vaccine authorized and out-of-pocket cost*

151 Three HPV vaccines have been licensed in Europe: bivalent, quadrivalent, and nonavalent marketed as
152 Cervarix®, Gardasil 4® or Silgard®, and Gardasil 9®, respectively. In most areas, two out of the
153 three vaccines were marketed (Table 1).

154 HPV vaccine was delivered free of charge for the target population in 28/32 areas. No out-of-pocket
155 cost was reported for recipients in all areas with high VCR. On the other hand, specific out-of-pocket
156 costs were observed in three (3/4) very low VCR areas (Greece, Poland, and France). In Greece,
157 vaccines have been delivered free of charge since 2016 through universal access to healthcare
158 services [17]. Before 2016, the policy implemented included free access to HPV vaccine only for girls
159 whose parents were employed, and therefore covered by a health insurance plan. In Poland, HPV
160 vaccine is at full out-of-pocket cost for individuals, as only mandatory vaccines are free of charge. In
161 France, the national health insurance reimburses 65% of the cost; a complementary private insurance
162 (CPI) might refund up to 35% of the total cost, depending on whether people subscribe to a CPI or
163 not. Approximately 95% of French people subscribe to a CPI and could get a refund, usually after
164 having paid for the vaccine [18].

165 *Regulatory aspects*

166 Parental consent before vaccination was not reported at the time of investigation for Romania, and
167 was not required in one (1/10) high VCR area (the United Kingdom) and in three (3/6) moderate VCR
168 areas (the Czech Republic, Luxembourg, and the Netherlands). In areas requiring parental consent
169 before vaccination (27/31), this consent was mandatory for girls under 18 years old in 23/27 areas,
170 and for girls under 16 (alternatively 15 or 14) years old in 4/27 areas, i.e. Portugal and Switzerland
171 (Slovenia or Latvia, respectively). Parental consent had to be written in 16/26 areas (one area with
172 missing type of consent).

173 Providing information about HPV vaccine to recipient prior to administration was reported as
174 mandatory in 26/32 areas.

175 ***Vaccination practical implementation***

176 All geographical areas with high VCR (10/10) have implemented a structured HPV vaccination
177 programme [19–23]. Six areas with moderate VCR (6/7), i.e. the Czech Republic, Denmark, Ireland,
178 Italy, Luxembourg, and the Netherlands, had implemented a structured HPV vaccination programme
179 [9,10,19,20].

180 Among areas with low VCR, three areas (3/4, i.e. Belgium-Walloon-Brussels, Latvia, and Slovenia) had
181 implemented a structured vaccination programme, while HPV vaccination was opportunistic in
182 Germany [20]. Finally, among areas with very low VCR, HPV vaccination was mainly opportunistic
183 (3/4), except for Bulgaria where a structured HPV vaccination programme started in 2012 [10].

184 In areas where HPV vaccination was part of a structured programme, prescription (if any was
185 required), dispensing, and administration of the vaccine occurred mostly at the same place and at the
186 same time. In contrast, in all areas where HPV vaccination was opportunistic, except for Germany,
187 prescription, dispensing, and administration occurred both at different places and at different times.
188 For example, in France and Greece, parents or girls have to make an appointment with a physician to
189 get an HPV vaccine prescription; obtain the vaccine from a community pharmacy; and then take
190 another appointment with their physician for administration of the vaccine.

191 Vaccination practical implementation steps are described in Table 2.

192

193

194 *Medical prescription*

195 Medical prescription was mandatory in 19/32 areas. Mandatory prescription was less frequent in areas
196 with high VCR (4/10) than in areas with very low VCR (4/4).

197

198 *Vaccination settings*

199 As previously observed for vaccination policies, vaccination practical implementation steps were
200 usually homogeneous at a national level, but could vary across geographical areas of a country, e.g.
201 vaccination settings. Subnational differences in vaccination settings were observed in five countries
202 (Belgium, Italy, Portugal, Spain, and Switzerland).

203 Areas with high VCR have implemented HPV vaccination with both dispensing and administration of
204 the vaccine in school or in public health centres. Indeed, school immunisation was offered in eight
205 (8/10) areas with high VCR.

206 By contrast, vaccination was administered in private practices or public community health clinics in
207 four (4/4) areas with very low VCR.

208

209 *Dispensing of the vaccine*

210 Vaccines were purchased collectively by the country and distributed by local structures in charge of
211 administering the vaccine, purchased by the physicians in private practices for later administration, or
212 purchased individually by patients in pharmacies and reimbursed by their health insurance companies.
213 In areas with high VCR, HPV vaccines were more often systematically dispensed at the place where
214 they were administered, i.e. in vaccination settings (9/10), than in areas with very low VCR (2/4).

215

216 *Invitations and reminders*

217 Invitations and reminders for HPV vaccine dose were used in 10/10 areas with high VCR, in 5/7 areas
218 with moderate VCR, and in 2/4 areas with low VCR. No invitations or reminders were used in the four
219 very low VCR areas.

220 Different types of reminders were used: for example, systematic phone call from public health centres
221 before the vaccination due date (Italy) or letter to unvaccinated girls (Portugal and the Netherlands).

222

223 ***HPV vaccination in males***

224 HPV VCR data in males was not published for in any area under investigation. HPV vaccination policies
225 and practical implementation in males are presented in Table 3.

226

227 *HPV vaccination policies*

228 A total of 10/32 areas recommended HPV vaccination in males: 1/10 area (UK) with high VCR in
229 females, 4/7 (the Czech Republic, Ireland, Italy, and Switzerland) with moderate VCR, 2/4 (France
230 and Poland) with very low VCR, and 3/7 (Austria, Croatia, and Cyprus) with no VCR. In Germany, only
231 Saxony had a gender neutral approach.

232 HPV vaccination was either recommended for all males (7/10), in a gender neutral approach, or for
233 males from specific subgroups (3/10, i.e. the United Kingdom, Ireland, and France). Specific
234 subgroups consisted of men who have sex with men (MSM), HIV-positive men, and men with other
235 immunodeficiency disorders.

236 HPV vaccine was free of charge for target groups in six (6/10) areas, i.e. Austria, Croatia, the Czech
237 Republic, Italy, Switzerland, and the United Kingdom. In France and Ireland, it was free of charge in
238 specific settings only.

239

240 *HPV vaccination practical implementation*

241 HPV vaccine was administered in schools, public health clinics, or in private practices for males with a
242 medical prescription in all countries, except for Cyprus and Croatia (8/10). It was dispensed in
243 vaccination settings in all countries, except for France; indeed, when administered in private practices
244 in France, the vaccine had first to be dispensed by pharmacies.

245 Reminders were sent to males in Italy only.

246

247 **Discussion**

248 In this comprehensive overview of HPV vaccination coverage, policies and practical implementation in
249 Europe, HPV VCR was monitored in females but not in males in most of the countries, and showed
250 wide variations. Variations of respective policies and practical implementation were also observed and
251 compared across countries to help identify those associated with higher VCR.

252 ***Variation of HPV VCR***

253 One third of included areas had high VCR, and one quarter had low to very low VCR in females, with
254 no clear North-South or East-West gradient. Due to lack of publicly reported standardised European
255 surveillance, data on HPV VCR were very difficult to collect, though they might be useful to monitor
256 the impact of HPV vaccination policies and practical implementation across Europe. Indeed, in their
257 recent commentary about sustainability of HPV vaccination programmes, Vorters and Van Damme
258 [24] reported monitoring of HPV VCR as critical to ensure its sustainability. According to the WHO
259 [25], variation of vaccination coverage rate across EU/EEA countries is not observed for other vaccines
260 like diphtheria-poliomyelitis-tetanus vaccine (VCR>90%) or measles vaccine (VCR>80%). Although
261 disease-related factors may partly explain the VCR differences between vaccines, these data suggest
262 that there may be a substantial room for improvement across Europe for HPV vaccination, especially
263 considering the objective set by the WHO of 90% HPV VCR by 2030.[8] Seven areas had no VCR data
264 to report, which was sometimes attributed to a recent implementation in the national immunisation
265 programme (Estonia, Lithuania), and sometimes to a lack of a monitoring system (Croatia, Slovakia).

266 ***HPV vaccination policies and practical implementation***

267 HPV vaccination policies varied widely across included areas. In areas with high HPV VCR in females,
268 HPV vaccination was recommended in females at the age of 10-13 years. In areas with very-low HPV
269 VCR, HPV vaccination was recommended in older girls (age 11-15). Several factors might explain this
270 finding. Vaccination initiation at an earlier age is known to be associated with higher vaccine
271 completion rate [26]. Moreover, a French study among 279 general practitioners in 2011 showed that
272 81% of them were in favour of HPV vaccination although 29% of them felt that the target age (14
273 years old) was a barrier mainly related to their perceived need to discuss sexual activity with

274 adolescent girls [27]. In this study, half of the general practitioners favourable to HPV vaccination
275 reported that they would prefer vaccinating girls earlier to avoid such discussion [27]. Discussions
276 about sexual activity with their daughter have also been reported as a barrier to HPV vaccination in
277 mother. [28] Accordingly, HPV vaccination at an earlier age might help both general practitioners and
278 parents disconnect discussion about sexual activity from discussion about HPV vaccine.

279 Implementation of a structured programme was more frequently observed in areas with high or
280 moderate VCR, and vaccination was mainly opportunistic in areas with very-low VCR. HPV vaccination
281 practical implementation also varied widely across included areas. In areas with high VCR, vaccination
282 settings were mainly school-based, HPV vaccine was always dispensed onsite, and reminders were
283 used. In areas with very-low VCR, HPV vaccine was mainly administered in clinics or in private
284 practices, but was not always dispensed onsite and reminders were never used. Accordingly, despite
285 the probable variation across the HPV vaccination programmes implemented in areas with high VCR,
286 facilitating access to HPV vaccination by increasing onsite vaccine availability, sending reminders, and
287 relying on schools as the main setting to administer the vaccine might be associated with improved
288 HPV VCR. Some of these results have already been confirmed by interventional studies. [29–31]

289 A recent literature review of interventions to improve HPV vaccine uptake indeed highlighted three
290 categories that have proven effective: informational, behavioural, and environmental interventions.
291 [29] First, informational interventions, delivered individually or collectively, that aim to increase
292 knowledge on HPV-related diseases are associated with a modest improvement in the vaccination
293 uptake during implementation of the intervention. However, their effect fades away after they are
294 discontinued. Our results could not support the effectiveness of information provided to recipients on
295 HPV vaccine, probably because this information was mandatory in most countries, and was provided
296 even though it was not mandatory in all countries. [29] Second, behavioural interventions, such as
297 patient-targeted or provider-targeted reminders, have proven highly effective. [29,30] Interestingly,
298 provider-targeted interventions are successful in initiating HPV vaccination whereas patient-targeted
299 interventions are more successful in vaccination completion. [32] Third, environmental interventions
300 including school-based vaccination are frequently associated with high VCR as they increase access to
301 vaccination [29,30]. This was noticeable in Switzerland, where vaccination practical implementation

302 and delivery differed by cantons: higher VCR were observed in cantons where the school health
303 services were involved in the delivery of the vaccine for the target group.[33] Outside of Europe,
304 school immunisation programmes were also particularly successful in achieving high HPV VCR in
305 Australia. [34] Availability of the vaccine onsite is also associated with improved HPV vaccine uptake.
306 [35]

307 In males, HPV vaccination was rarely recommended in included countries, VCR was not available, and
308 the related policies and practical implementation steps were too heterogeneous to draw any
309 conclusion about the possible association between HPV vaccination policies or practical
310 implementation in males and HPV VCR in females. However, the fact that we could not find any data
311 on HPV VCR in males suggests that HPV VCR was not monitored in males as it was in females, and
312 might call for better surveillance.

313 As described by Elfström et al. [20], an easily accessible European benchmark on HPV vaccination
314 policies and their practical implementation combined with a European standardised monitoring of HPV
315 VCR might help countries struggling with persistent very-low HPV VCR to implement effective HPV
316 vaccination policies. In this respect, immunisation information systems (or immunisation registries)
317 might be useful to monitor HPV VCR at a European level [36]. This is of particular importance since
318 WHO targets a 90% HPV VCR for complete schedule for girls by the age of 15 by 2030, in order to
319 move towards cervical cancer elimination within a century. [8]

320 ***Additional barriers to achieve high HPV VCR***

321 Some of the HPV vaccination policies and practical implementation processes might hinder countries
322 with very-low VCR from improving their VCR.

323 First, cost of HPV vaccine might be a barrier to achieve high HPV VCR. Indeed, HPV vaccine was free
324 of charge in countries with high VCR in our overview. On the opposite, individuals were charged out-
325 of-pockets costs in countries with very-low VCR. For instance, in France, out-of-pocket costs were the
326 highest in the main vaccination setting, i.e. private practices, though it might not be the main reason
327 for very-low VCR in France. Indeed, French individuals from higher social class reported more often
328 than individual from lower social classes a negative opinion about HPV vaccine [37] or hesitancy about

329 vaccines [38]. In Greece, the observed VCR was very low. The financial crisis in 2012 was likely to at
330 least partly explain the concomitant drop observed in VCR, as the number of uninsured persons
331 increased at this time. [39] However, universal access to healthcare has been established in 2016,
332 and might be associated with a future increase of the VCR in the coming years. Similarly, the very-low
333 VCR observed in Poland might result from the out-of-pocket cost in private practices.

334 Second, mandatory medical prescription might also be a barrier to achieve high HPV VCR. Indeed,
335 medical prescription was mandatory for the dispensation of HPV vaccine in all countries with very-low
336 VCR, which can complicate the process by adding additional steps to obtain the vaccine. In countries
337 with high VCR, mandatory medical prescription was less frequently observed in our overview.

338 Last but not least, some countries were faced with HPV vaccine controversies leading to VCR drop.
339 From 2013, Denmark experienced growing media attention on HPV vaccine safety and an increase of
340 reported alleged adverse events following immunisation. Furthermore, a television programme
341 broadcasted in 2015 featuring girls with disabling symptoms allegedly linked to HPV-vaccination
342 caused a marked decline in vaccine uptake to under 50%. Denmark had successfully addressed these
343 issues by running an informational campaign, mostly online, featuring a website and a Facebook page
344 [40]. Similarly, in Ireland, misinformation was spread by some lobby groups on social media in 2015,
345 and a documentary on national television has raised parental concerns resulting in VCR decline. [41]
346 Ireland rapidly organised an informational campaign targeting parents and health professionals, which
347 led to an increase in HPV vaccine uptake in the school year 2017/2018.[42]

348 **Limitations**

349 Causality to link HPV policies and practical implementation steps to VCR is difficult to establish due to
350 the cross-sectional, descriptive, and ecological design of this overview. In addition, the wide range of
351 political and legislative settings observed in Europe might have led to various interpretations of the
352 variables we aimed to collect, leading to information bias. However, the use of a standardised form
353 with a clear definition of each one of the collected variables probably limited this bias. In addition, to
354 overcome this potential limitation, the form, once prefilled with the literature and websites' review
355 results, was sent to the experts; tailored additional information was provided to the experts if needed.

356 Another information bias might have occurred when assessing HPV VCR in some countries, because of
357 the variety of methods used to estimate VCR across countries [20]. However, validation of the results
358 by native experts increased the probability that the data adequately reflected the vaccine uptake in
359 the target country.

360 Finally, we focused only on HPV vaccination policies and practical implementation. However, HPV VCR
361 is also influenced by sociocultural factors and individual characteristics, as reported in Switzerland
362 [33], that might explain part of the observed VCR variation.

363 **Conclusion**

364 This study explored health policies and practical implementation processes that might explain variation
365 in HPV vaccination uptake across 31 European countries. We observed that structured vaccination
366 programmes targeting females early in adolescence and free of charge vaccine administration were
367 more frequently observed in high VCR countries than in very-low VCR countries, which therefore may
368 be important factors for achieving high vaccine uptake. Facilitating access to HPV vaccination by
369 increasing onsite vaccine availability, sending invitation and reminders to attend for vaccination, and
370 relying on schools as the main setting to administer the vaccine might also be associated with
371 improved HPV VCR. Monitoring of both HPV vaccination policies and practical implementation and HPV
372 VCR at a European level, as well as sharing experiences between countries might be of major public
373 health relevance to achieve consistently high HPV VCR across Europe.

374

375 **Authors' contribution**

376 NT, CP and NA initiated the study. NHNG and NA drafted the protocol, that was reviewed by
377 all authors. NHNG collected the data, which were double checked when needed by NA. CP
378 contacted all national representatives. NHNG interviewed the national representatives. NHNG
379 analysed the data, under the supervision of NA. All authors helped interpret the data. NHNG
380 and NA drafted the manuscript, which was reviewed by all authors.

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540

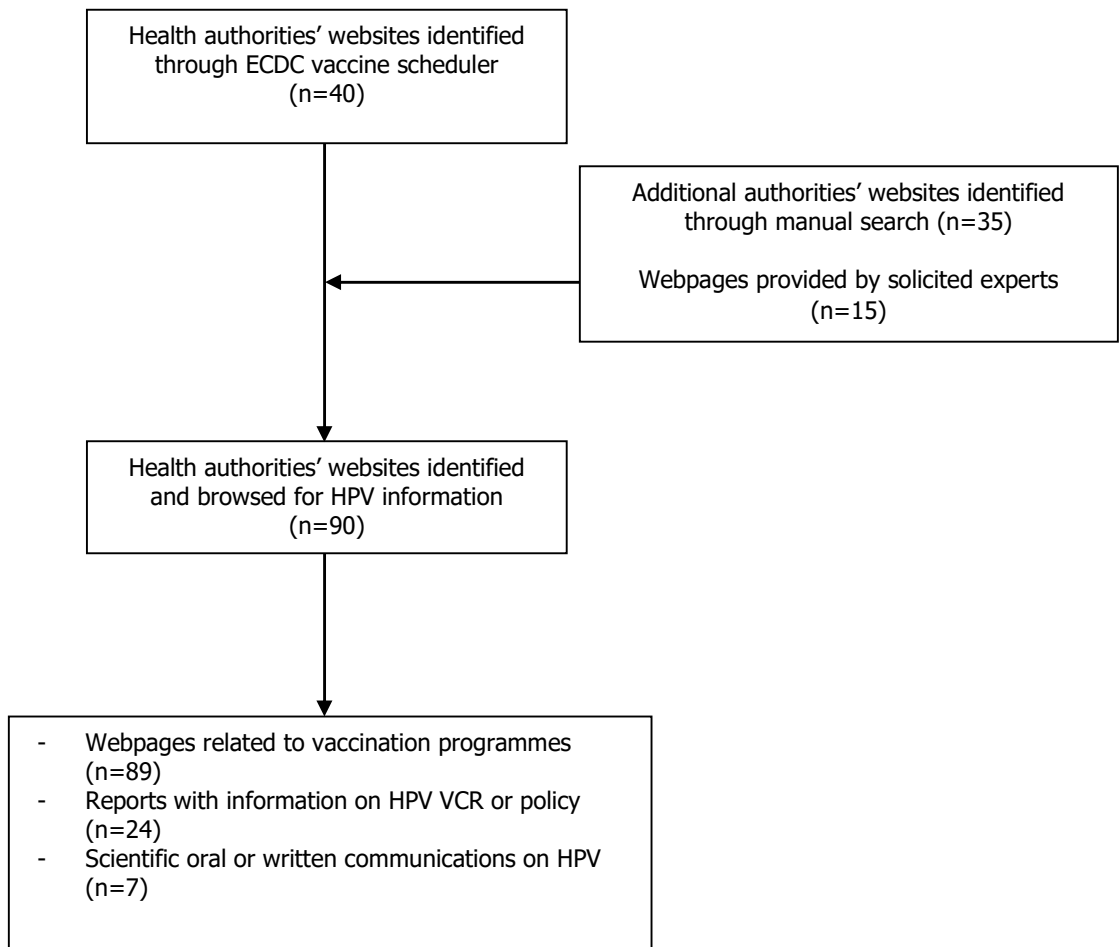


Figure 1: Flow chart of health authorities' websites selection

Notes: ECDC: European Center for Disease and Control, HPV VCR: Human Papillomavirus vaccination coverage rates

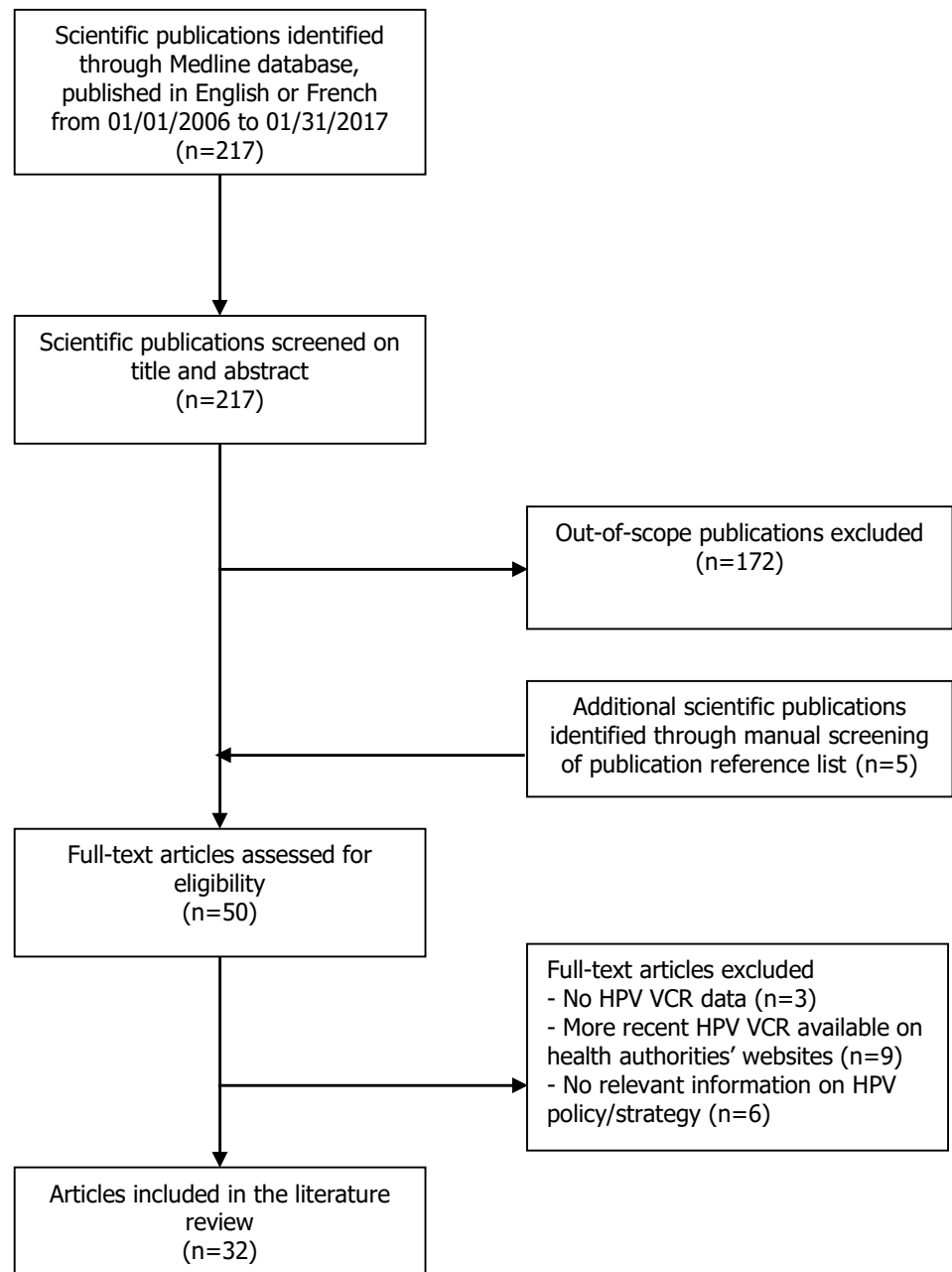
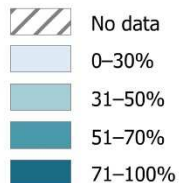


Figure 2: Flow chart of scientific publications selected for the literature review

HPV VCR for 1 dose(*) or complete schedule, from 2010-2017:



(Year of VCR)

Target age (years) recommendation for female vaccination

Vaccination settings:
 © School immunisation
 © Private practice
 Pu Public or community health clinics

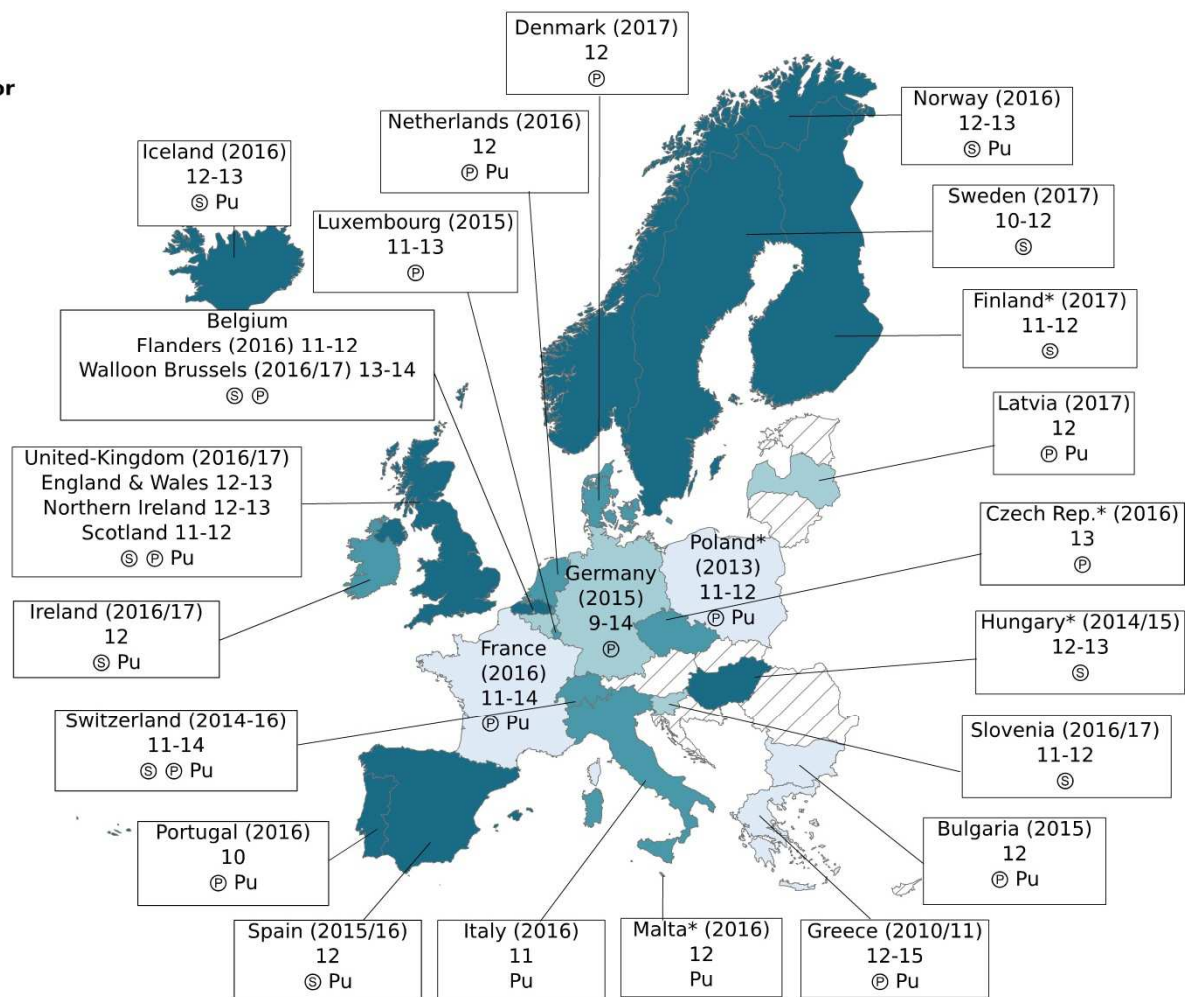


Figure 3: Human Papillomavirus vaccination coverage rates (HPV VCR) in target agegroups in females and vaccination settings in European countries, 2010-2017

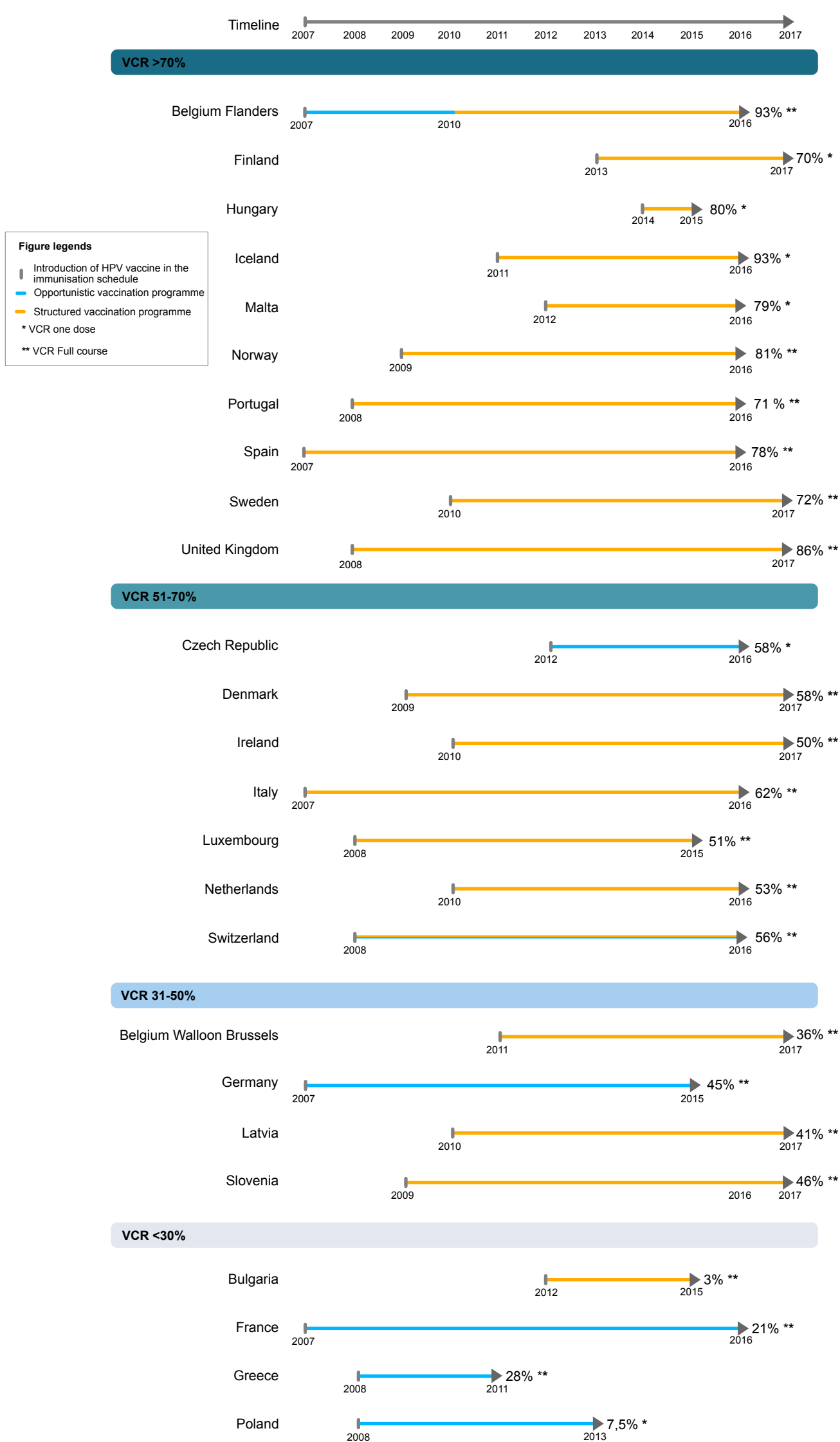


Figure 4: Timeline of Human Papillomavirus vaccination policies and vaccination coverage rates in European countries, 2010-2017

HPV VCR 51-70%											
Czech Republic	2012	F, M	13	No catch up	2v*, 4v, 9v	2v free of charge for target, 4v partially reimbursed for target, 9v not reimbursed for target	N	NA	NA	2016 :58 % ^q for 13yo	NR
Denmark	2009	F	12	NA ^p	(2v, 4v) ^s 9v*	Free of charge for target and catch-up group	Y	O	Y	2017: 59% for birth cohort 2004 68% for birth cohort 2003 83% for birth cohort 2002	2017: ^q 39% for birth cohort 2004 43% for birth cohort 2003 58% for birth cohort 2002
Ireland	2010	F, M	12	NA ^r	2v, 4v*, 9v	Free of charge for target	Y	W	Y	NR	2016/2017: ^s 50.4% for for birth cohort 2003
Italy	2007	F, M	11	NR ^t	2v*, 4v*, 9v*	Free of charge for target	Y	W	Y	2016: 69% for birth cohort 2003	2016: ^u 62% for birth cohort 2003
Luxembourg	2008	F	11-13	15-18	2v*, 4v	Free of charge for target and catch-up group	N	O	Y	2015:62% for 12yo	2015:51% ^v for 14yo
Netherlands	2010	F	12	NA ^w	2v*, 4v, 9v	Free of charge for target	N	NA	Y	NR	2016:53% ^x for 14 yo
Switzerland	2008	F, M	11-14	15-19 (20-26) ^y	2v*, 4v*	Free of charge for target, catch-up and complementary group within the cantonal programme ^z	Y for girls<16 yo	W ^{aa}	Y	2014-2016:59% at 16yo	2014-2016: 56% ^{bb} at 16yo
HPV VCR 31-50%											
Belgium Walloon Brussels	2011	F	13-14	15-18	2v*, 4v, 9v	Free of charge for target 10% cost for catch-up group	Y	W	Y	2016/2017: 43.3% at 12-13yo	2016/2017: ^{cc} 36.1% at 12-13yo
Germany	2007	F ^{dd}	9-14	15-17	2v*, 4v*, 9v*	Free of charge for target and catch-up group	Y	O	N	2016/2017: survey in process NR	2015 : 31.3% at 15yo ^{ee} 44.6% at 17 yo
Latvia	2010	F	12	13-17	2v*, 4v, 9v	Free of charge for target and catch-up group	Y for girls <14 yo	O	Y	2017: 50% for 12 yo	2017: 41% ^{ff} for 12 yo
Slovenia	2009	F	11-12 y (grade 6 primary school)	13-14	2v, 4v*, 9v	Free of charge for target and catch-up group	Y, for girls <15 yo	W	Y	NR	2016/2017: 46.4% at 11-12yo ^{gg}

HPV VCR ≤ 30%											
Bulgaria	2012	F	12	13-25	2v, 4v, 9v	Free of charge for target	Y	–	–	NR	2015: 2.68% ^{hh} at 12
France	2007	F, M	11-14	15-19	2v*, 4v*	Free of charge (in public vaccination centres or sexual health centres)	Y	O	Y	2017: 26% 2016: 24% at 15yo	2017: NR ⁱⁱ 2016: 21% at 16yo
						Partial reimbursement in private practices: - free of charge for target group and catch up if they have a complementary private insurance - 35% left to recipients if no complementary private insurance					
Greece	2008	F	12-15	15-18	2v*, 4v*, 9v*	Free of charge for target and catch-up group	Y	O	N	NR	2010-2011: 27.6% at 18-20 yo 23% at 21-26 yo ^{jj}
Poland	2008	F, M	11-12	13-18	2v*, 4v*, 9v*	Full cost of vaccine and consultation ^{kk}	Y	O	Y	2013: 7.5% for 11-13yo ^{ll}	NR
No HPV VCR data											
Austria	2014	F, M	9-12	13-15	4v, 9v*	Free of charge for target (9v) Reduced cost for catch-up group (4v)	Y	W	Y	NR	NR
Croatia	2016	F, M	9-25 in 2016 ^{mm}	9-25	2v*, 4v*, 9v*	Free of charge for target and catch-up group	Y	W	Y	NR	NR
Cyprus	2007	F, M	12-13	14-45	2v, 4v*, 9v	Free of charge for target in school Full cost for catch-up group	Y	W	Y	NR	NR
Estonia	2018	F	12	Actual implementation programme catch up until 2020 for 13-14yo	9v	Free of charge for target and catch up	Y	W	Y	NR	NR
Lithuania	2016	F	11	NR	2v, 4v*, 9v	Free of charge for target	Y	W	N	NR	NR
Romania	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Slovakia	2010	F	12	No catch up	2v*, 4v*, 9v*	Partial reimbursement by the health insurance company: 90% of the total price left for the recipient for 2v 94% of the total price left for the recipient for 4v	Y	W	Y	NR	NR

Notes:

Abbreviations: F: Female; M: Male; NA: not applicable; NR: not reported; 2v: Cervarix®; 4v: Gardasil® or Silgard®; 9v: Gardasil ® 9; Y: Yes; N: No; O: Oral; W: Written;

*recommended in the national immunization programme;

**Two or three doses immunisation, depending on the country and year;

a Geert Top MD. "The HPV vaccination programme in Flanders". Available at: <http://www.vaccineconfidence.org/wp-content/uploads/2017/06/HPV-London-20170607TopG.pdf>. Accessed June 06th 2018.

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c National Institute for Health and Welfare Finland. "HPV vaccine coverage reports 2017". Available at: <https://thl.fi/roko/rokotusrekisteri/hpvraportit2017>. Accessed June 06th 2018.

d Recommended for boys 9-26 yo but not in national immunisation programme

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h Catch-up at the programme implementation for girls who completed 17 years old between 2009 and 2011

i Portugal General Directorate of Health. "National Programme of Vaccination". Available at: <https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/programa-nacional-de-vacinacao/relatorios-e-publicacoes.aspx>. Accessed June 06th 2018.

j Catch-up at the programme implementation for most regions

k Written consent when vaccinated in school settings

l Spanish Government. "Human papillomavirus vaccination coverage". Available at:

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^m Regional catch-up campaigns for women up to 26 yrs in some counties. Catch-up at the programme implementation in 2012–2016 for girls 13–18 yrs (born 1993–1998).

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o Catch-up at the programme implementation in 2008-2011 for girls 13-17yo

^p Denmark had offered mass catch-up: Girls born in 1993, 1994, and 1995 were offered HPV-vaccination in 2008-2010 and again in 2013-2015, this time also including cohorts of girls born in 1996 and in 1997. In addition, young girls born between 1985 and 1992 were offered HPV-vaccination in 2012-2013.

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r Ireland Health Protection Surveillance Centre. "HPV Immunisation Uptake Statistics". Available at: <http://www.hpsc.ie/a-z/vaccinepreventable/vaccination/immunisationuptakestatistics/hpvimmunisationuptakestatistics/>. Accessed June 06th 2018.

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^t Target age for catch up groups varies across the regions.

u Italy Ministry of Health. "Human papillomavirus vaccination coverage at 31/12/2016" http://www.salute.gov.it/imgs/C_17_tavole_27_allegati_iitemAllegati_0_fileAllegati_itemFile_1_file.pdf. Accessed June 06th 2018.

v Luxembourg Health Directorate, Epidemiology and Statistics department. "HPV vaccination coverage in Luxembourg". 18/12/2017

w Catch up at the programme implementation in 2009 for girls 13-16yo

x National Institute for Public Health and the Environment. "Vaccination rate and annual report National Vaccination Program Netherlands 2016". Available at:

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y Catch-up for 15-19yo, complementary recommendation for 20-26yo for indicated cases

^z The vaccination is free of charges and covered by the health insurance for the recommended groups if administered within a canton programme. All cantons have a programme but the conditions vary between cantons.

aa Written consent was required in school programs

bb Swiss Public Health Office. "Vaccination Coverage". <https://www.bag.admin.ch/bag/fr/home/themen/mensch-gesundheit/uebertragbare-krankheiten/impfungen-prophylaxe/informationen-fachleute-gesundheitspersonal/durchimpfung.html>. Accessed November 16th 2017

cc STATISTIQUES DE COUVERTURE VACCINALE EN 2IÈME SECONDAIRE. Enquête de couverture vaccinale en Fédération Wallonie-Bruxelles 2016-2017. Dr A.Vermeeren, Dr F.Goffin. (

^{dd} Recommended for males 9-26yo in Saxony region of Germany, partial reimbursement rate depending on health insurance

ee Rieck T, Feig M, Siedler A, Wichmann O. Aktuelles aus der KV-Impf-surveillance – Impfquoten ausgewählter Schutzimpfungen in Deutschland. *Epid. Bull.* 2018;1:1 – 14 | DOI 10.17886/EpiBull-2018-001.1

ff Latvia Centre for Disease Prevention and Control. "Overview of immunization ". <https://www.spkc.gov.lv/lv/statistika-un-petijumi/infekcijas-slimibas/epidemiologijas-bileteni1/parskats-par-imunizaciju-cetur>. Accessed June 06th 2018.

gg Slovenia National Institute of Public Health. "analysis of implementation of vaccination in Slovenia in 2016". Available at: http://www.nijz.si/sites/www.nijz.si/files/uploaded/porocilo_cepjenje2016.pdf. Accessed June 06th 2018.

hh Bulgarian National Immunisation Programme for primary prevention of cervical cancer 2017-2020. Available at: <http://www.strategy.bg/FileHandler.ashx?fileId=9261>. Accessed June 06th 2018.

ii Public Health France. "Human papillomavirus vaccination coverage". <http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-prevention-vaccinale/Couverture-vaccinale/Donnees/Papillomavirus-humains>. Accessed June 06th 2018.

jj Sample of High education students (seven Universities and two Technological Educational Institutes.)_ Source: Donadiki, Elisavet M., Rodrigo Jiménez-García, Valentín Hernández-Barrera, Pilar Carrasco-Garrido, Ana López de Andrés, and Emmanuel G. Velonakis. "Human Papillomavirus Vaccination Coverage among Greek Higher Education Female Students and Predictors of Vaccine Uptake." *Vaccine* 30, no. 49 (November 19, 2012): 6967–70. doi:10.1016/j.vaccine.2012.09.028.

^{kk} Free of charge when a local vaccination programme is implemented, for example in like in Czerniejewo municipality, where girls could get vaccinated at school. Profilaktyka zakażeń wirusem brodawczaka ludzkiego HPV dziewcząt 12. i 13.letnich zamieszkałych na terenie Gminy Czerniejewo" - Programy polityki zdrowotnej realizowane na terenie gminy Czerniejewo - Zdrowie - Gmina Czerniejewo

ll Data obtained by survey on girls attending the first classes of post-secondary schools in Zgorzelec_ Source: Owsianka, Barbara, and Maria Gańczak. "Evaluation of Human Papilloma Virus (HPV) Vaccination Strategies and Vaccination Coverage in Adolescent Girls Worldwide." *Przegląd Epidemiologiczny* 69, no. 1 (2015): 53–58, 151–55.

mm Due to low uptake during the year of introduction of the programme, the target age was extended.

Table 2: HPV vaccination practical implementation in females in European countries, 2010-2017

Countries	Mandatory medical prescription	Vaccination settings	Dispensing of the vaccine	Reminders
HPV VCR>70%				
Belgium Flanders	Y ⁱ	Private practice; Schools	Vaccination settings; Pharmacies	Y
Finland	N	Schools	Vaccination settings	Y
Hungary	Y	Schools	Vaccination settings	Y
Iceland	N	Health care centres; Schools	Vaccination settings	Y
Malta	N	Public or community health clinics	Vaccination settings	Y ⁱⁱ
Norway	N	Public or community health clinics; Schools	Vaccination settings; Pharmacies	Y
Portugal	N	Public or community health clinics; Private practices ⁱⁱⁱ	Vaccination settings	Y ^{iv}
Spain	Y	Primary health centres; Schools	Schools; Pharmacies (for primary health centres)	Y
Sweden	N	Schools	Vaccination settings	Y
United Kingdom	Y ^v	Public or community health clinics; Private practices; Schools	Vaccination settings	Y
HPV VCR 51-70%				
Czech Republic	Y	Private practices	Vaccination settings; Pharmacies	N
Denmark	Y	Private practices	Vaccination settings	Y ^{vi}
Ireland	Y ^{vii}	Public or community health clinics; Schools	Vaccination settings	Y
Italy	Y	Public or community health clinics	Vaccination settings	Y
Luxembourg	Y	Private practices	Pharmacies	Y
Netherlands	N	Public or community health clinics; Private practices	Vaccination settings	Y
Switzerland	Y	Public or community health clinics; Private practices; Schools	Vaccination settings; Pharmacies ^{viii}	NR ^{ix}
HPV VCR 31-50%				

Belgium	Y	Private practices; schools ^x	Vaccination settings; Pharmacies	Y
Walloon- Brussels				
Germany	Y	Private practices	Vaccination settings ^{xi} ; Pharmacies	N
Latvia	Y	Public or community health clinics; Private practices	Vaccination settings; Pharmacies (if prescription out of the National Immunisation programme)	N
Slovenia	N	Schools	Vaccination settings	Y
HPV HPV VCR ≤30%				
Bulgaria	Y	Public community health clinics; Private practices	Vaccination settings; Pharmacies	NR
France	Y	Public or community health clinics; Private practices	Public or community health clinics; pharmacies	N
Greece	Y	Public or community health clinics; Private practices	Pharmacies	N
Poland	Y	Public or community health clinics; Private practices ^{xii}	Vaccination settings; Pharmacies	N
No HPV VCR data				
Austria	Y	Public health clinics; Private practices; Schools	Vaccination settings; Pharmacies	N
Croatia	N	Public or community health clinics; Private practices	Vaccination settings	
Cyprus	N	Private practices; Schools	Vaccination settings; Pharmacies	Y
Estonia	Y	Public or community health clinics; Private practices	Public or community health clinics; Pharmacies	Y
Lithuania	Y	Public or community health clinics; Private practices	Vaccination settings	N
Romania	NA	NA	NA	NA
Slovakia	Y	Private practices	Pharmacies	N

Notes:

Abbreviations: Y: Yes; N: No; NA: not applicable; NR: not reported

i Except in schools

ii The invitation letter came with an appointment scheduled during off-school hours in the health centre.

iii Available in private practices if there is a convention with Ministry of Health

iv Reminders were emailed to unvaccinated patients with delays in vaccination schedule

v Except in schools

vi In 2014, there was a National intervention of written reminders using the Danish Vaccination Register that were sent out at age 14 if doses of vaccines were missed by that age

vii Except in schools

viii Vaccine delivery depends on cantons

ix Variation by regions

^x Free choice for the schools to offer HPV vaccination, and approximately 30% schools in Wallon Brussels didn't offer HPV vaccination.

xi If the recipient is statutory insured, the vaccine is available at the GP. If the recipient is privately insured, the vaccine has to be collected at the pharmacy.

xii In case of regional programme, vaccination can be administered in schools.

Table 3: HPV vaccination policies and practical implementation for males and other specific at-risks groups in European countries in 2017

Countries	HPV vaccination policies					
	Target groups	Specific groups	Target age	Type of vaccine used	Out-of-pocket cost	Mandatory medical prescription
Austria	All	NA	9-12	4v, 9v	Free of charge for 9-12, Reduced cost for 13-15, Full price >15	Y
Croatia	All	NA	≥9	2v, 4v, 9v	Free of charge for target	N
Cyprus	All	NA	9-25	2v, 4v, 9v	Full cost for vaccine and consultation	N ¹
Czech Republic ^{§§§}	All	NA	13	2v*, 4v, 9v	2v free of charge for target, 4v partially reimbursed for target group 9v not reimbursed Full cost of the vaccine and consultation for the other groups.	Y
France [§]	S	MSM <26 yo HIV-positive aged 11-19 yo Transplanted individuals aged 9 -19 yo	NA	4v	Free of charge (in public vaccination centres or sexual health centres) Partial reimbursement in private practices ²	Y

¹ The vaccines are bought and stored by the physicians.

*Used in the national immunisation programme

§ Countries with very low HPV VCR in females

§§ Countries with moderated HPV VCR in females

§§§ Countries with high HPV VCR in females

² Free of charge for target group and catch-up if they have a complementary private insurance, 35% left to recipients if no complementary private insurance

Ireland ^{§§§}	S	MSMHIV-positive	NA	4v*	Free of charge in Gay Men's Health Service sexually transmitted infection Clinics ³	Y
		Fanconi anaemia patients Transplanted individuals	NA	4v	Full cost of the vaccine and consultation ⁴	Y
Italy ^{§§§}	All	NA	11	4v, 9v	Free of charge for target	Y
Poland [§]	All ⁶	NA	≥11	4v, 9v	Full cost of the vaccine and consultation	Y
Switzerland ^{§§§}	All	NA	11-26	2v, 4v	Free of charge ⁷	Y
United Kingdom ^{§§§§}						
England ⁹	S	MSM	NA	4v	Free of charge	Y
Wales, Northern Ireland, Scotland	S	MSM	NA	4v	Free of charge	Y

Notes: Abbreviations : NA: not applicable; NR: not reported; All: all males; S: Specific groups; MSM : men who have sex with men ; 2v: Cervarix®; 4v: Gardasil® or Silgard®; 9v: Gardasil ® 9; Y: Yes; N: No;

3 not provided to General Practitioners (GPs) from the National Immunisation Programme, but GPs could procure from private source and provide free of charge

4 HPV vaccine could be procured from national programme (specific request required) if medically indicated, but administration charges would normally be applied

5 During 2017: Introduction of the HPV vaccination programme for eleven-year-old males with the start of the active call for the 2006 cohort

6 Also recommended to MSM who had not been vaccinated before and to HIV-positive aged 9-26 yo

7 The vaccination is free of charge and covered by the health insurance for the recommended groups and if administered within a cantonal programme. All cantons have a programme but the condition varied between cantons

8 Vaccination settings depends on regions

9 England had been offering HPV vaccines for MSM from April 2018, following a successful HPV implementation pilot project in genito-urinary medicine and HIV clinics from June 2016 to March 2018