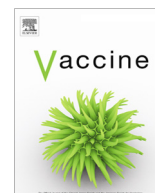


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Human papillomavirus vaccination coverage in Luxembourg – Implications of lowering and restricting target age groups

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ABSTRACT

Background: In Luxembourg, a national Human Papillomavirus (HPV) vaccination programme was introduced in 2008, targeting 12–17 year old girls offering a choice of bivalent or quadrivalent vaccine free of charge. In 2015, the programme was changed offering the bivalent vaccine only to 11–13 year old girls. The aim of this study was to evaluate the HPV vaccination coverage, to assess the impact of age target changes and compare vaccination coverage to other European countries.

Methods: Anonymous HPV vaccination records consisting of individual vaccine doses obtained free of charge in pharmacies between 2008 and 2016 were extracted from the Luxembourgish Social Security database. Additional aggregate tables by nationality and municipality were analysed.

Results: Of the target cohort of 39,610 girls born between 1991 and 2003 residing in Luxembourg, 24,550 (62.0%) subjects obtained at least one dose, 22,082 (55.7%) obtained at least two doses, and 17,197 (43.4%) obtained three doses of HPV vaccine. The mean age at first dose was 13.7 years during 2008–14 and 12.7 years in 2016 after the age target change. Coverage varied significantly by nationality ($p < 0.0001$): Portuguese (80%), former Yugoslavs (74%), Luxembourgish (54%), Belgian (52%), German (47%), French (39%) and other nationalities (51%). Coverage varied also by geographical region, with lower rates (<50%) noted in some Northern and Central areas of Luxembourg (range: 38% to 78%).

Conclusion: Overall HPV vaccination coverage in Luxembourg is moderate and varied by nationality and region. The policy changes in 2015 did not have a substantial impact except lowering age at initiating vaccination. Options to improve coverage deserve further investigation.

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1. Introduction

The recognition that cervical cancer is etiologically linked with persistent human papillomavirus (HPV) infection, [1,2] has led to the development of various cervical cancer preventive programmes, including screening and vaccination [3]. In 2006, the first HPV vaccine (Gardasil) was approved in the United States and the European Union [4]. This quadrivalent vaccine targets genotypes 6, 11, 16 and 18. Genotypes 16 and 18 account for approximately 70% of all cervical cancers, whereas genotypes 6 and 11 are the main cause of genital warts [5–7]. In 2007, a bivalent HPV vaccine (Cervarix) was introduced to the market for the primary prevention of genotypes 16 and 18. Since 2015, a nonavalent vaccine (Gardasil 9) has become available in Europe targeting nine HPV genotypes (6,

11, 16, 18, 31, 33, 45, 52, 58) [8]. By 31 March 2017, globally 71 countries have introduced national HPV vaccination programmes including 26 countries in Europe [9]. By the end of 2014, 47 million female subjects received HPV vaccines worldwide [10]. Recent studies show a significant reduction of vaccine-associated genotypes and protection from cervical lesions in vaccinated girls [11–14]. Several countries reported a decrease in incidence of genital warts following the introduction of national HPV vaccination programmes [15–17]. Moreover, the significant reduction of genotypes 31, 33, and 45 not contained in vaccines suggests a degree of cross-protection [12,18–20]. HPV vaccination has the potential to prevent cervical cancer and related deaths worldwide [21].

In Luxembourg, the national HPV vaccination programme started in March 2008 targeting 12–17 years old girls [22]. The programme aimed to deliver three doses, ideally, before the onset of sexual activity. When girls were 12 years old, they automatically received an information letter from the National Health Insurance and a brochure advising them to get vaccinated by their physician

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of choice prescribing either bivalent or quadrivalent vaccine. An invitation letter and information brochure were provided in four languages (Luxembourgish, German, French and Portuguese). Vaccines were typically administered as three intramuscular injections over 6 months. The parents then collected the prescribed vaccine doses from the pharmacy free of charge.

Following the updated 2014 WHO/EMA recommendation [23], during the spring of 2015, the national vaccination policy was changed limiting vaccination to girls aged 11–13 years with two doses of bivalent vaccine over a 6 month interval. Girls aged 14–17 years were still eligible to receive three doses of bivalent or quadrivalent vaccine free of charge until the end of 2015.

The main purpose of this study was to evaluate the HPV vaccination coverage in Luxembourg based on the analysis of National Health Insurance records and compare it to the situation of countries in Europe with a similar health system.

2. Materials and methods

2.1. Study population

The study was performed using the Luxembourgish Social Security database, covering approximately 95% of the resident population, the remaining fraction consisting mainly of European Union institutions employees and their family members, which have their own social security system. The information contained in the database consists of patient characteristics, medical consultations, interventions, prescriptions, laboratory tests and hospital discharge data.

2.2. Data extraction and pseudonymisation

HPV vaccination records consisting of individual vaccine doses obtained in pharmacies between 2008 and 2016 were requested from the Social Security Inspection (<http://www.mss.public.lu/acteurs/jgss/index.html>) who have direct access to the database. For data protection purposes, the Social Security Inspection changed personally identifiable social security numbers to pseudonymised identifiers for the study investigators so that no further linkage to other health information was possible. The data set in comma separated text format was transferred from the Social Security Inspection to the study team by secure file transfer.

2.3. Characteristics of the dataset

The data set analysed in this study consisted of pseudonymised personal identifiers, age at first vaccine dose acquisition, interval in days between first, second and third dose, year of birth, calendar year of obtaining the first, second and third dose, vaccine type, medical speciality of the prescribing physician and total number of doses obtained. For reasons of data protection only aggregate tables by nationality and municipality could be obtained. Nationality here refers to the nationality information recorded in the national registry of physical persons at the time of data extraction. In Luxembourg, nationality concept refers to citizenship. Additionally, we received the following socioeconomic data aggregated at commune level from the public statistics portal (<http://www.statistiques.public.lu/>): average monthly income, unemployment rate and frequency distribution of nationalities.

2.4. Statistics

Statistical analysis was performed in Stata 14.0 (StataCorp, USA). We used Pearson's correlation coefficient to assess the association between continuous variables. For the coverage calcula-

tions girls born after 2004 year were excluded from the analysis, since they had potentially not yet completed the full vaccination schedule.

2.5. Ethics and data protection

The study was approved by the National Research Ethics Committee (CNER 201501/02) and the National Data Protection Commission (CNPD 288/2016).

3. Results

At the end of 2016, 39,610 females born between 1991 and 2003 years were resident in Luxembourg according to the Social Security database.

3.1. Vaccination coverage

Of that cohort 24,550 (62.0%) obtained at least one dose of HPV vaccine, 22,082 (55.7%) obtained at least two doses, and 17,197 (43.4%) obtained three doses. 70.0% of girls initiating vaccination completed a full schedule with three doses and 89.9% completed a partial schedule with two doses. The lowest vaccination coverage with at least one dose was observed in girls born in 1991, significantly increasing in the following birth cohorts. The highest vaccination coverage was noted for the cohort born in 1998, with at least one, two and three dose coverages of 70.1%, 64.5% and 58.1%, respectively (Fig. 1).

3.2. Vaccine uptake over time

The total number of obtained vaccines per year varied substantially over time. It was highest in the first year after vaccine introduction, then stabilized until the policy changes in 2015 produced another substantial increase (Fig. 2a). Approximately half of the women born between 1991 and 1996 obtained their first dose in 2008 (Fig. 2b). The high vaccination uptake during the first year was due to larger number of age groups eligible for the first time (Fig. 2b). Despite the reduced target age range in 2016, the total number of girls initiating vaccination was similar to 2014 (Fig. 2).

3.3. Vaccination coverage by region and nationality

Coverage varied geographically ranging from 38.4% to 78.6%, and was lower in the North and Centre of Luxembourg. Communes with the highest coverage are located in the Eastern and South-western parts of the country (Fig. 3). Coverage was found to be significantly associated with nationality ($p < 0.0001$), highest for Portuguese (80%) or former Yugoslavs (74%), intermediate in

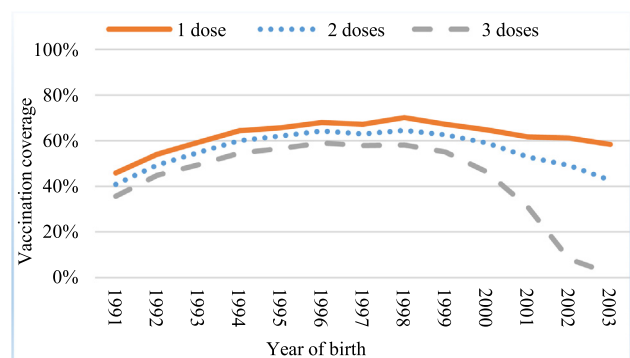


Fig. 1. HPV vaccination coverage per birth cohort.

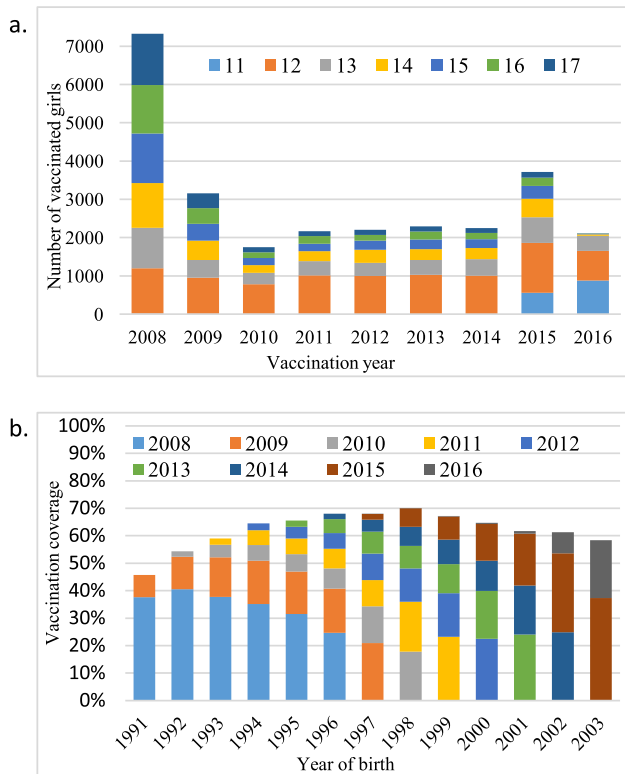


Fig. 2. a. Number of girls vaccinated per year and age. b. Proportion of obtained vaccines (at least one dose) per birth cohort and year of vaccination.

Luxembourgish (54%), Belgian (51%) and other nationalities (51%) and lowest among the German (47%) or French (39%) residents (Fig. 4).

3.4. Vaccination following policy change and vaccine distribution

The mean age at first dose was 13.7 years during 2008–14 and 12.7 years in 2016 after the age target change. During 2008–2014, 59.4% and 40.6% of vaccinated women obtained quadrivalent and bivalent vaccine, respectively. During 2015–2016, 7.7% of vaccinated women obtained quadrivalent vaccine and 92.3% obtained bivalent vaccine. The second and third doses were obtained after 90 (range: 0–1943) and 154 (range: 0–2076) days on average, respectively. The total number of obtained vaccine doses during 2008–2016 was 63,829 consisting of 53.5% (34,139) quadrivalent and 46.5% (29,690) bivalent vaccine doses.

3.5. Speciality of vaccine prescribers

During 2008–2014, 54.2% of doses were prescribed by general practitioners, 30.5% by pediatricians and 14.5% by gynecologists. During 2015–2016, 47.7%, 44.2% and 6.5% of vaccine doses were prescribed by general practitioners, pediatricians and gynecologists, respectively. The mean age of girls vaccinated by general practitioners was 13.9 years, 12.9 years for girls vaccinated by pediatricians and 14.6 years for girls vaccinated by gynecologists (Fig. 5). Fig. 5b shows that role of pediatricians in prescribing HPV vaccine increased considerably for recent birth cohorts.

3.6. Vaccination coverage and socioeconomic status

The vaccination rate was not correlated with population density, average monthly income, unemployment rate or proportion

of foreigners. A borderline correlation result was observed between vaccination and proportion of French residents in a commune ($p = 0.04$, data not shown).

4. Discussion

In this study, we assessed HPV vaccination coverage rates in Luxembourg for the girls born between 1991 and 2003 years based on the national health insurance data. Highest coverage and highest completion rate was observed in girls born in 1998, with at least one, two and three dose coverages of 70.1%, 64.5% and 58.1%, respectively. Overall, vaccination coverage of at least one dose was 62.0%, at least two doses was 55.7%, and three doses was 43.4%. Coverage varied significantly by nationality and geographical region.

In Luxembourg, all childhood vaccines are administrated by private and hospital physicians. The coverage of HPV vaccination is relatively low compared to other vaccinations: immunisation coverage for other childhood vaccines is approximately 95% [24]. One of the reasons behind the difference in vaccination rates could be physicians' hesitancy to recommend HPV vaccine. Physician's hesitancy to vaccinate has already been known in the past to have caused localised outbreaks of measles in the northern Luxembourg [25]. We also observed lower HPV vaccination rates in some northern parts of the country. Introducing HPV vaccination at school level would represent a major challenge, as there is currently no public infrastructure or personnel for vaccine administration.

HPV vaccination coverage with at least one dose appears to be higher in Luxembourg than in other European countries without school-based vaccination programmes. In neighbouring Germany and France, one dose coverage is lower than 50% [26–28]. However, in England and Scotland, where school-based delivery strategy is used, coverage of one dose is 91% and 94% and coverage of three doses is 86% and 81%, respectively [29]. In the Flanders region of Belgium where school-based system coexists with opportunistic vaccination by health centres, one dose coverage reached 90% [30]. Denmark achieved a high vaccination coverage through general practitioners, but coverage decreased significantly lately due to vaccine hesitancy [31,32]. Several studies suggest that coverage in a school-based delivery system is higher than in non-school-based system [30,33–35]. Switching to school-based vaccination in Canada led to a significant increase of coverage [36].

In Luxembourg, schedule completion rates for two doses was 90% and for three doses 70%, partly influenced by the change in vaccination programme in 2015 offering only two doses (cf. girls born in 2002 and 2003 in Fig. 1). In France only 49% of girls who initiated vaccination completed the three-dose schedule [28]. In Germany and Belgium approximately 80% of girls completed the full schedule [27,37]. High completion rates were observed in Denmark reaching 92% [31]. Some recent studies suggest that one or two doses schedules provide similar levels of protection than three dose schedules [38].

Our study suggests HPV vaccination in Luxembourg was associated with nationality and regional factors. In particular, HPV vaccination uptake was significantly lower in German and French residents and higher in Portuguese and former Yugoslav residents, which somewhat similar to vaccination coverage for other childhood vaccines [24]. This mirrors to a large extent vaccination acceptance in these respective countries – lower than 50% in France and Germany and higher than 80% in Portugal [10,26–28]. From former Yugoslav countries, coverage estimates are only available from Slovenia (70–74%) [39]. Many studies have shown ethnicity to be an import determinant of vaccination acceptance [31,40]. Interestingly, in the Netherlands HPV vaccination uptake is significantly lower in immigrants [41]. Similarly in France, lower

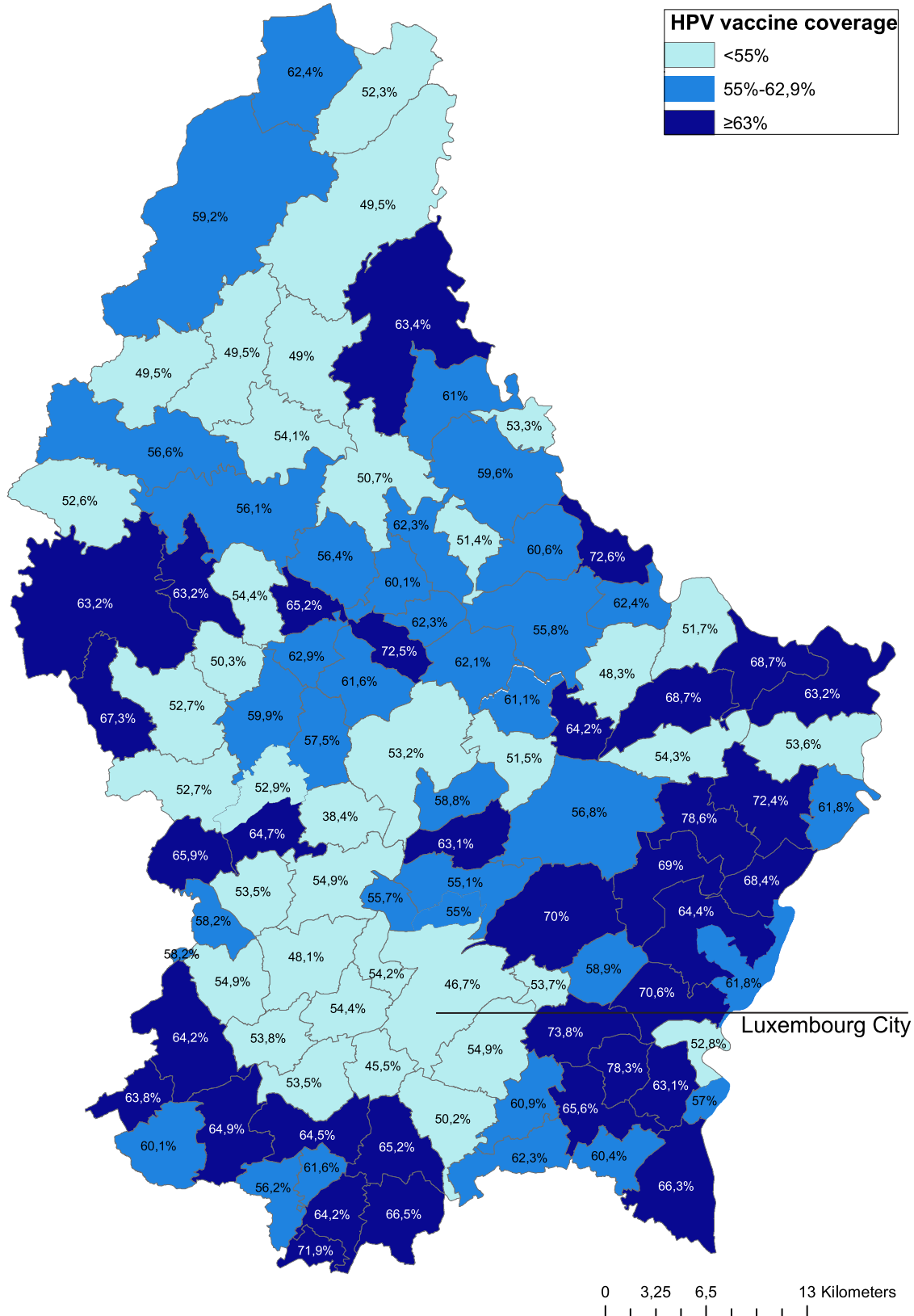


Fig. 3. HPV vaccine coverage (at least one dose) by geographic region.

vaccination coverage was associated with high migration rate and percentage of foreign population [28]. Sociodemographic inequalities in HPV vaccination coverage were observed in countries with low coverage or in countries without school-based programmes

[30,36]. In Luxembourg, vaccination did not appear to be correlated with average income, unemployment rate or distribution of foreign nationalities at the geographical level of communes, although a borderline correlation was observed with the proportion of French

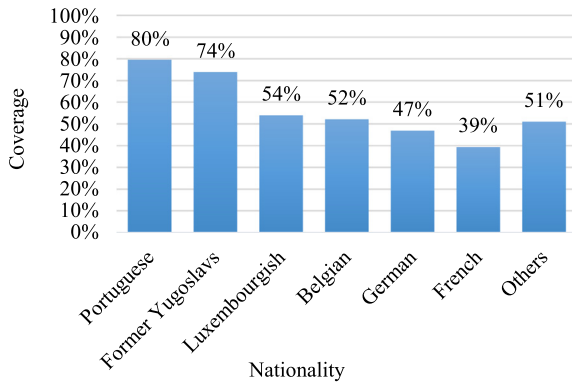


Fig. 4. HPV vaccine coverage (at least one dose) by nationality.

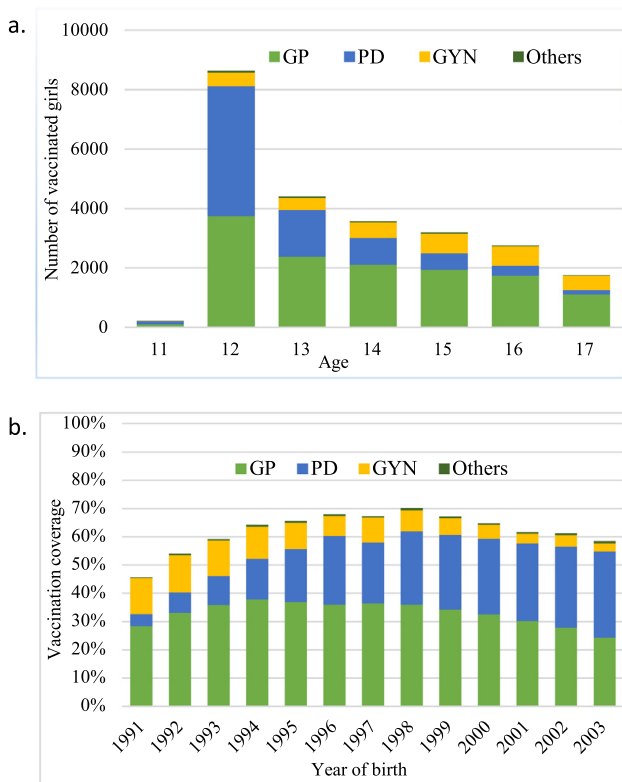


Fig. 5. a. Number of girls vaccinated (at least one dose) by specialty of the prescribing physician and age. **b.** Proportion of prescriber's specialty per birth cohort (at least one dose). Abbreviations: GP, general practitioner; PD, pediatrician; GYN, gynecologists.

residents which account for approximately 6% of the total population in Luxembourg.

Since 2009–2010, the number of vaccine doses used in Luxembourg decreased yielding a stabilisation of the vaccine coverage up to cohort 1998 and decreasing in the following cohorts. It is expected that birth cohorts 2004–2005 will have a higher coverage than birth cohort 2003, considering that girls of 11–13 years are better vaccinated in 2015–16 than the years before. However, the birth cohort coverage will not increase, since girls older than 13 years no longer have the opportunity to get vaccinated after 2016. The lack of catch up vaccination could be problematic, since Luxembourg has a high immigration rate (more than 100,000 migrants arriving in last five years). Incoming teenage international protection seekers do not currently have an opportunity to receive HPV vaccine.

An interesting impact of the policy change is that vaccine prescriber specialty is changing towards more pediatricians and GPs and less gynecologists. This may suggest that it is easier for parents to vaccinate girls when they are pre-teen visiting GPs or pediatricians, rather than teenagers visiting gynecologists who are less involved in administering vaccines in general. An advantage of a shift of HPV vaccination towards younger groups is that the proportion not yet exposed to HPV infection becomes higher. In addition, higher antibody titers were observed in younger girls aged 9–14 years compared to older girls [28]. Therefore, these younger cohorts will be more protected against HPV-related disease than those who were vaccinated at age 16–18 in the first years of the programme.

To our knowledge, this is the first study assessing HPV vaccination coverage in Luxembourg. To be able to monitor the impact of HPV vaccination in the future it will be crucial to link HPV vaccination records with cervical cancer screening and cancer registry data [42], completed with targeted HPV genotyping of samples [14]. Estimation of the impact of HPV vaccination in Luxembourg is the aim of the ongoing Papillux research project, results of which will be published shortly.

Ways to improve coverage include simplifying the logistics of vaccine prescription and acquisition: currently parents who want to vaccinate their girls need first to visit a prescribing doctor, obtain the vaccine at the pharmacy and then return to the physician for vaccine administration. It would be more efficient if doctors would be able to keep a stock of vaccines from a central pharmacy as for other childhood vaccines. Moreover, since physicians are very influential in the parents' decision making process, it is important to develop strategies addressing doctor's hesitancy, targeting both pediatricians and GPs. Educational activities targeting physicians and specific population groups with lower vaccination coverage could, for example, help to increase uptake. Additionally, it would be feasible to provide catch up vaccination of international protection seekers who are above the narrow vaccination target age group as part of their routine medical check up after registration.

Nevertheless, HPV vaccination coverage in Luxembourg remains moderate and while challenging, increasing coverage for residents and migrants of all nationalities and in all regions should be an important public health priority.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

Ardashel Latsuzbaia and Joël Mossong analysed the data and wrote the paper. Marc Arbyn and Steven Weyers advised and reviewed the manuscript. All authors listed approve the submission and confirm that neither this manuscript nor any part of it has been published or is under consideration for publication elsewhere.

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Ethical approval

The study was approved by the Comité National d'Ethique de Recherche (CNER # 201501/02, Version 1.1) and was authorized by the Commission Nationale pour la Protection des Données (CNPD 288/2016).

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