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Review

Human papillomavirus (HPV), HPV-associated oropharyngeal cancer, and HPV vaccine in the United States—Do we need a broader vaccine policy?

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ABSTRACT

Background: Human papillomavirus (HPV) is a sexually transmitted infection (STI) of global importance; it is the most prevalent STI in the United States, with strains causally linked to oropharyngeal and other cancers. Efforts to prevent HPV have been made to varying degrees by policies implemented by different state governments; however, HPV and associated oropharyngeal cancer continue to show increasing incidence rates in the US.
Design: A narrative review based on search on SciVerse, PubMed/Medline, Google Scholar, and EMBASE databases, as well as literature/documents from the World Health Organization, Centers for Disease Control and Prevention, American Cancer Society, National Conference of State legislatures, and the U.S. Department of Health and Human Services relevant to HPV and HPV vaccine policy in the US.
Results: Vaccination has proved to be a successful policy in the US, and an extant recommendation aimed at preventing HPV and associated cervical and other anogenital cancers is the routine use of HPV vaccines for males and females. However, HPV vaccines are presently not recommended for preventing oropharyngeal cancer, although they have been shown to be highly effective against the HPV strains that are most commonly found in the oropharynx. And while there is a history of successful vaccine mandate in the US with resulting decrease in occurrence of infectious diseases, implementing HPV vaccine mandate has proved to be very unpopular.
Conclusions: With emerging evidence of the efficacy of the use of the HPV vaccine in preventing oral-HPV, more focus should be put on extending HPV vaccine to present oral HPV infection and oropharyngeal cancer. Also, implementing a broader HPV vaccine policy that include mandating HPV vaccines as a school-entry requirement for both sexes may increase vaccine use in the US for the greater good of the public.

Contents

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1. Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract, and an estimated 630 million people are affected by it worldwide [1]. HPV has been causally linked to several cancers and a number of asymptomatic lesions, including cervical, anogenital, and oropharyngeal/head and neck cancers, as well as genital warts [2]. Virtually 100% of all cervical cancers worldwide are known to be caused by HPV [2,3]. Cervical cancer is the third most prevalent cancer among women worldwide, with almost 300,000 deaths resulting annually [4]. HPV was initially thought to account for at least 23% of cases of oropharyngeal cancer [5]. However, more recent studies indicate that at least 70% of the oropharyngeal cancer incidence in the US in the last three decades may be causally linked to HPV [6,7]; and unlike cervical cancers, oropharyngeal cancer affect both men and women. Oropharyngeal cancer is the 6th most prevalent cancer worldwide and 13th in the United States [8]. There are at least 40 different strains of the HPV virus that can infect the genitals of both sexes [9]; of these strains, the most common and highest risk for oropharyngeal cancer are HPV 16 (almost 90% of all HPV-positive oropharyngeal cancers) and 18 [9,10].

HPV is also the most prevalent sexually transmitted infection (STI) in the United States [11]. A nationally representative sample of American adults between 2009 and 2010 estimates oral HPV to be about 7%; and an earlier survey of American females aged 14–59 years estimates genital HPV prevalence to be about 27% [12,13]. The adolescent population has the highest cumulative prevalence rate of HPV in the US, and it is estimated that nearly all sexually active Americans, males and females, may be infected by the virus in their lifetime [14].

Several articles and reviews have been published that discuss the role of HPV in oropharyngeal cancer. This narrative review was written to focus on current HPV prevention and control policies in the US, while making a case for more primary prevention efforts in relation to HPV-associated oropharyngeal cancer. This article will briefly highlight the disparities associated with HPV and oropharyngeal cancer, and recommends broadening the current HPV vaccine recommendations and use. It will draw lessons from a historical precedent that was set in the era of small pox and polio vaccines in recommending vaccine mandate, and then discuss potential unintended consequence that could arise as a result of the recommended policy.

2. Disparities associated with HPV infection and oropharyngeal cancer

Many of the disparities associated with oral HPV infection and oropharyngeal cancer are based on gender, socioeconomic status, race and ethnicity. Men are more than twice likely to be infected than women [12], and oral HPV infection appears to be more prevalent among Africa-Americans than Whites [12]. For HPV positive oropharyngeal cancer, there are more White patients than African-Americans, but the latter have worse overall survival [15,16].

3. Current policies

There is presently no federal law preventing and controlling HPV infection; however, since the FDA approval of HPV vaccines (Gardasil and Cervarix), and the 2006 recommendation by ACIP (Advisory Committee on Immunization Practices), there have been various moves by states to enact and implement laws that will provide some form of HPV prevention or control, ranging from public education about the disease, legislation on funding, HPV/cervical cancer screening, and mandating children to take up the vaccine routinely as they enter into middle school [17]. (See Table 1) As of July 2012, at least 42 states (including Washington D.C.) have introduced some form of legislation regarding HPV/HPV vaccine [17,18].

On their own, each of these policies (better public education, requiring insurance companies to fund the HPV vaccine/HPV vaccine funding legislation; non-mandated option of HPV vaccine with parental approval; and mandating the HPV vaccine for middle school entry) above has merits, but a broader policy involving HPV vaccine use and access would complementary, and may prove to be a more robust solution to the HPV problem.

For example, creating better public education and awareness about HPV among stakeholders (parents, teachers, and adolescents)

Table 1
U.S. states with HPV vaccine legislation (2006–2012).[a]

HPV vaccine legislation	States
Introduced legislation to educate the public about HPV and/or the HPV vaccine; and/or introduced legislation to further study the issues surrounding the HPV vaccine	Arizona, Colorado, Connecticut, Hawaii, Florida, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Mississippi, Missouri, Minnesota, Nebraska, New Jersey,[b] New Mexico,[c] New York, North Carolina,[b] North Dakota,[b] Pennsylvania, Tennessee, Texas,[b] Utah, Washington, Wisconsin
Enacted public education legislation	Colorado, Indiana, Iowa, Maryland, Minnesota, New Jersey,[b] New York, North Carolina, North Dakota, Texas,[b] Utah,[b] Washington[b]
Introduced legislation to fund and/or require insurance companies to fund the HPV vaccine	Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kentucky, Louisiana, Maine, Massachusetts, Mississippi, Nevada,[b] New Jersey, New Mexico,[b] New York, Oregon, Pennsylvania, Rhode Island,[b] South Dakota,[b] Texas, Vermont, Virginia
Enacted HPV vaccine funding legislation	California, Colorado, Illinois, Iowa, Maine, Nevada, New Mexico, New York,[b] Rhode Island,[b] South Dakota[b]
Non-mandated option of HPV vaccine with parental approval, pending funding	South Carolina[d]
Introduced legislation to mandate the HPV vaccine for middle school entry	California, Colorado, Connecticut, Washington D.C., Florida, Georgia, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, Minnesota, Mississippi, New Mexico,[e] New York, Ohio, Oklahoma, South Carolina, Texas, Vermont, Virginia,[b] West Virginia
Approved HPV vaccine mandate	Texas,[f] Washington D.C.,[b] Virginia[b,g]

[a] Sources: [21,22].
[b] Legislations signed into law.
[c] Legislation adopted.
[d] Legislation vetoed by governor, veto sustained by the house.
[e] Legislation vetoed.
[f] Legislation signed into law but overridden.
[g] Legislation facing repeal.

is a primary preventive measure described in the literature as a simple and potentially effective policy that that could improve uptake of HPV preventive measures [19–22]. However, the general public's health knowledge of HPV remains low [23]. Also, many parents and other adult gatekeepers or guardians are not comfortable discussing issues related to sex with their children or wards, and often restrict access to important resources for the promotion of safer sex and other sex-related information from them [24–29]; conversely many children do not feel comfortable discussing issues related to sex with their parents; and some parents would prefer school based sex education [24–29]. However, sex education is presently not taught in all elementary and middle and high schools in America [30]; yet almost half of American children between the 9th and 12th grade are sexually active [31], and almost a two-third of high school students become sexually active by their 12th grade [31]. Another strategy that has been explored is providing secondary preventive measures like screenings. The Pap smear, for example, has been a mainstay for detecting HPV and cervical cancer cases in women. It has been shown to be very effective, reducing incidence rates up to 80% in some populations with appropriate follow-up [32]. The importance and effectiveness of such screening is underlined by the fact that cervical cancer, which was once a leading cause of death in women in United States, now kills fewer than 5000 people annually [33]. Unlike the Pap smear however, there is presently no universally accepted, evidence-based screening protocol for oropharyngeal cancer and oral HPV, even though several methods and techniques have been developed [34].

4. Recommendation and a lesson from history

Since HPV is largely preventable, vaccinating against the most common strain of the virus in the oral mucosa (HPV-16) may prevent future cancers and deaths if boys and girls of middle school age, irrespective of possession of health insurance, are provided with full coverage for the HPV vaccine. This is because the HPV vaccines available (Gardasil and Cervarix) have been demonstrated to be highly effective in HPV-16 related lesions in both sexes [35,36]. However, the licensed vaccines are presently not administered to prevent oral HPV infection, even though HPV-16 remains the most common in the oral cavity, just as it is in the uteri cervix. Since HPV-16 is a common factor between cervical and oropharyngeal cancer, biological plausibility would suggest that if oral HPV rates decrease due to vaccine use (if or when approved for oral cancer prevention), incidence of HPV-associated oropharyngeal cancer would likely decrease too. There are indications that the present speculation based on biological plausibility may soon change to actual science, given the very recently published result of a clinical trial that demonstrated that the HPV vaccine may be very efficacious in preventing oral HPV, especially HPV-16 [37]. In addition, HPV negative oropharyngeal cancers, mainly attributable to smoking (and a synergy between smoking and drinking), are largely preventable, and are already decreasing in the population [6,7]. Thus, devising a strategy for providing universal HPV vaccine coverage holds the promise of significantly contributing to decrease in HPV-associated cancers in the US, including oropharyngeal cancer, if (or when) the vaccine coverage is extended for oral HPV prevention. There is abundant literature that describes the role school entry requirements have played in increasing vaccine coverage in general [38–45]. Perhaps, having state governments mandate school-entry administration of the HPV vaccine could potentially bridge the disparity gap in HPV infections, and ensure that disadvantaged populations are catered to [40]. Since health care systems are different, another school-related policy that may have a strong impact on HPV vaccination rate in the US is school-based vaccination. Routine school based HPV vaccination has already been proven to be very effective and as well as successful, as shown by reports from Australia, where such a program has been implemented, with 72% of the quadrivalent vaccine coverage between 2007 and 2010, as well as a suggestion of an increasing herd immunity [46]. For females 12–17-year-old in Australia, there have been 77% reduction in genital warts among vaccine eligible females and 44% decrease among unvaccinated age-matched males [47]. There are also indications of a decline in high-grade cervical intraepithelial neoplasia (CIN2+) incidence among females less than 18 years old; just as it has been reported in the UK [48,49]. The success of this strategy is also seen in the case of HPV vaccine uptake rate in Rwanda, Africa, where 93% of HPV vaccine coverage has been achieved, mainly through school-based vaccination of girls in their 6th grade [50].

However, the policy situation in the US may make the dream of mandating HPV vaccine without exceptions a challenging proposition. First, although there have been calls in Europe to mandate the HPV vaccine [51], the reality remains that there has not been any successful vaccine mandate of any kind, mandates without any exception, in the last 100 years or so [40]. In addition, of the 42 states (including D.C.) that have initiated an HPV/HPV vaccine related policy since 2006, only Virginia, and D.C have mandated female sixth graders to be immunized against HPV, and the bill in Virginia is facing a repeal, just as it happened in Texas a few years earlier [17,40,51,52]. (See Table 2 for the differences between the school-mandate in Virginia and in D.C.) In all 42 states including D.C., the focus of the HPV/HPV vaccine bills has mainly been females between 9 and 26 years old. There has been no legislative action so far on the October 25, 2011 ACIP recommendation that young boys between 11 and 12 years of age be vaccinated against HPV [53]. Yet, males carry a high burden of the HPV infection and associated cancers, and play a significant role in transmitting the

Table 2
Virginia and Washington D.C. HPV vaccine mandate and specific provisions.[a]

Provision	Virginia[b]	Washington D.C.[c]
HPV vaccine-specific opt-outs	**Parents may refuse the vaccine for any reason plus education** Because HPV is not communicable in a school setting, a parent or guardian, at the parent or guardian's sole discretion, may elect for their child not to receive the HPV vaccine, after having reviewed materials describing the link between HPV and cervical cancer approved for such use by the Board. §32.1-46 D3	**Parents may refuse the vaccine for any reason plus limited education** The parent or legal guardian, at his or her discretion, has elected to opt out of the HPV vaccination program, for any reason, by signing a form prepared by the Department of Health that states the parent or legal guardian has been informed of the HPV vaccination requirement and has elected not to participate. §5
Target population	All girls entering sixth grade	All girls entering sixth grade
Effective date	October 1, 2008	January 1, 2009

HPV, human papillomavirus.
[a] Source: [52].
[b] An Act to amend and reenact §32.1-46 of the Code of Virginia, relating to requiring HPV vaccine.
[c] The HPV Vaccination Reporting Act of 2007, Bill B17-30.

Table 3
Does vaccine mandate work? Annual morbidity rates at the beginning of the 20th century in the US vs. mortality rates by 1998 for diseases with vaccine mandates.[a]

Disease	Average annual morbidity rates from the beginning of the 20th century onwards [actual year(s)]	Mortality rates by 1998	%Decrease
Smallpox	48, 164 (1900–1904)	0	100%
Diphtheria	175, 885 (1920–1922)	1	100%[b]
Poliomyelitis (paralytic)	16, 316 (1951–1954)	0	100%
Measles	503, 282 (1958–1962)	89	100%[b]
Mumps	152, 209 (1958)	606	99.6%
Rubella	47, 745 (1966–1968)	345	99.3%
Tetanus	1, 314 (1922–1926)	34	97.4%
Pertussis	147, 271 (1922–1925)	6279	95.7%

[a] Source: [61].
[b] Rounded to the nearest tenth.

virus to females [12,54], and although males do not develop cervical cancer, they can develop warts, oropharyngeal, anal, and penile cancers. Take anal cancer as an example. The Centers for Disease Control and Prevention (CDC) reports that men who have sex with men are about 17 times more likely to develop anal cancer than men who only have sex with women, and statistics show that the incidence of anal cancer is on the increase in the US [55,56]. The question therefore is when state legislators plan to add boys to the plan already in place, or being developed, for girls.

A challenge of mandating HPV vaccine is that it would require consent of parents or guardians, and many of them might hesitate to comply, either due to personal, cultural, or religious reasons [39,40,57]. However, one advantage of vaccination that has been suggested in the literature is that it directly protects, not only the person getting the vaccination, but his or her partner [54,58,59]. There is also a potential of cross-protection against other strains of HPV virus other than those the vaccine were made specifically for [60]. Only this option provides this unique, double-fold value among the current HPV prevention and control policies or strategies in place.

Vaccination has been heralded as a top 10 public health achievement of the 20th century [61] (Table 3). Indeed, history teaches a lesson in requiring compulsory vaccination, rather than just recommendations. A look at all the vaccines that have been the most successful in preventing deaths in the US show a vast difference in annual morbidity rates, pre- and post-vaccine mandate/school entry requirement [61] (Table 3). Two best examples of resounding success as a result of vaccine mandate are: one, the first and only human virus that has been completely eradicated worldwide, the small pox virus, eliminated in the late 1970s; a feat achieved by a combination of efforts, including several decades of mandates and enforcements in Europe and the US [62–68]; and two, the polio virus, which has been completely eliminated in the US and the entire Western Hemisphere, and almost completely eliminated worldwide, except a handful of countries left [41,44,69]. Note that it took decades of enforcing these mandates before success was achieved; in fact, a recent 50-year model suggests that less than 80% vaccine uptake is the very best that could be achieved in 50 years from the present HPV vaccine recommendation for girls, whereas a school-entry requirement or mandate would achieve 90% uptake in only 43 years [45]. The issue now would be whether we can borrow a leaf from our past to pass and enforce HPV school-requirement/vaccine mandate. A robust policy like this, albeit controversial, may be what is needed to prevent HPV and associated cancers.

5. Economics

There have been arguments about cost-effectiveness of the HPV vaccine, and it has been regarded as the costliest vaccine ever known to the human race [40,51]. Admittedly, paying up to $360 for a vaccine may be too steep for many Americans, especially those of lower socioeconomic status, hence the fear that mandating vaccines may do more harm than good to the already wide disparity gap in the US [12]. However, cost effectiveness may have to be put into perspective. Many of the cost-effectiveness studies do not account for the burden of other HPV-associated malignancies, like oropharyngeal cancer [6] (because as of yet, the HPV vaccines are not indicated for oral HPV infections), and genital warts (because of one the two HPV vaccines available does not protect against the strains of HPV that causes genital wart); thus underestimating the actual cost-effectiveness of the vaccine [6]. One study reports that non-cervical HPV related diseases may cost American between $160 million and $1.6 billion yearly [70], even though a single dose of the vaccine cost may cost up to $130 [71]; while another study indicates that costs associated with HPV infections, including genital warts and the sequelae run into $5 billion yearly [57]. And this is excluding associated psychosocial costs and quality of life issues that people with HPV infection and associated cancers have to deal with [72,73]. Although the vaccine itself may be expensive for some, disparity in uptake could be mitigated by the government through the Vaccine for Children Program (VFC) for those eligible [68,74,75]. It is evident that uptake of the HPV vaccine will always result in some kind of cost for both the government and individuals, whether HPV vaccine is mandated or not. This also makes a case, or justifies the need for testing the efficacy of the vaccine available in the market for non-cervical cancers, especially oropharyngeal cancer [72]. Since both vaccines available have been proven to be effective against the most common HPV strain in the oropharynx, vulva, vagina, anus, and penis; and the result of a clinical trial suggests that the HPV vaccines could be efficacious against oral HPV, especially HPV-16 [37], should not more vaccine efficacy studies focus on oropharyngeal and other non-cervical cancers, especially as it is being projected that HPV positive oropharyngeal cancer will have higher incidence than cervical cancers by the year 2020 [6,72]? Is there no wisdom in having a shift from focusing only on prophylactic HPV vaccination for cervical cancer, to the ever increasing oropharyngeal cancer, especially since there is presently no standard screening for oropharyngeal cancer [6,7]?

6. Unintended consequences

Like most other policies, a policy to vaccinate young boys and girls in the United States with the HPV vaccine may have some unintended consequences. One of such is the fear of potential side effects of the vaccines. So far, it is claimed by the FDA and the CDC, and pharmaceutical-industry sponsored clinical trials that the HPV vaccines are very safe and without serious vaccine-related adverse effects [35,53]. However, there are indications that many parents and guardians are still skeptical about vaccine safety [20,76]. In addition, since the vaccines are still relatively new in the market (the first was licensed for use in the United States only 7 years

ago); it is still possible that some side effects or adverse events may not become apparent until years later through extensive follow-up and prospective studies [77,78]. Already, there are reports through the Vaccine Adverse Events Reporting System (VAERS) in the US of some adverse events like hypersensitivity reactions, anaphylaxis, Guillain–Barre' syndrome, transverse myelitis, pancreatitis, and venous thrombo-embolism a few years after vaccine uptake [35,53,77].

There are also concerns about the morality of administering a vaccine that is supposed to prevent a sexually transmitted disease later in future life, and how acceptance of this vaccine would affect parental autonomy, infringe on right to self-determination and individual freedom, and the right to conscientiously object to a medical procedure based on religious values, personal circumstances and conscience; or whether it would increase sexual risk taking [57,77,79,80]. Along the same lines, and although unfounded, there are also concerns that encouraging children to accept a vaccine that protects against a disease that is not airborne but only sexually transmitted is implicitly encouraging sexual liberty in children [57].

There are also potential liability and other legal issues that could ensue. Although the American Academy of Pediatricians and the Centers for Disease Control consider the HPV vaccine very safe, there will likely be legal suits and compensations if the vaccine recipients or their families prove that they suffered serious adverse effects following vaccine uptake [51].

In addition to these concerns, there are fears about longevity of efficacy and possible waning of vaccine's protective ability; however, in the follow-up studies recorded thus far, there have not been any significant decrease in the clinical efficacy against HPV-16 and 18, thus such fears, for now, are rather precocious [71].

7. Conclusion

HPV is undoubtedly an important public health problem in the United States, as well as the rest of the world. It remains the most prevalent sexually transmitted infection in the US, and it is causally linked to several cancers and other disease conditions. Mandating HPV vaccination holds a lot of promise, as it could among other things greatly mitigate incidence of cervical cancer, and possibly other non-cervical cancers like oropharyngeal cancer in both men and women. Although there might be some unintended consequences of the vaccine uptake and its mandate, it seems to be an option for the greatest good of all, as mandatory vaccine coverage holds the potential of providing a double-fold protection for the person taking the vaccine and his or her future partner [72]. In addition, the American Academy of Pediatricians and the Centers for Disease Control and Prevention have repeatedly stressed that HPV vaccine are safe and that they continue to promote it as a vaccine that has the potential to prevent cancer and saves millions of lives, with more than 46 million doses of the quadrivalent vaccine already administered [81,82]. The Healthy People 2020 has oral cancer and oral health objectives, and these have direct bearing on HPV prevention and control [83]. Thus, as the government pushes for the elimination of health disparities in the society, encapsulated by the *Healthy People 2020* program, it will be critical to scrutinize what policies are in place at present to address highly preventable infections like HPV and its associated cancers, and possibly broaden the HPV vaccine policy to include using it to prevent oral HPV and HPV-associated oropharyngeal cancer as the science of vaccine efficacy against oral HPV emerges; as well as mandating HPV vaccine use for the appropriate age group. That may be the best way forward in achieving health for all in our society.

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References

[1] World Health Organization. Human Papillomavirus. http://www.who.int/vaccines/en/hpvrd.shtml [accessed 21.03.13].
[2] World Health Organization. Human Papillomavirus. http://www.who.int/nuvi/hpv/en [accessed 26.03.13].
[3] Garner EI. Cervical cancer: disparities in screening, treatment, and survival. Cancer Epidemiol Biomarkers Prev 2003;12:242s–7s.
[4] Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893–907.
[5] Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709–20.
[6] Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294–301.
[7] Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms. J Natl Compr Canc Netw 2011;9:665–73.
[8] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309–16.
[9] Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14:467–75.
[10] Ryerson AB, Peters ES, Coughlin SS, Chen VW, Gillison ML, Reichman ME, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998–2003. Cancer 2008;113(Suppl. 10):2901–9.
[11] Centers for Disease Control and Prevention (CDC). Human Papillomavirus (HPV). http://www.cdc.gov/hpv/ [accessed 28.03.13].
[12] Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States: 2009–2010. JAMA 2012;307(7):693–703.
[13] Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al. Prevalence of HPV infection among females in the United States. JAMA 2007;297:813–9.
[14] Moscicki AB. Impact of HPV infection in adolescent populations. J Adolesc Health 2005;37(Suppl. 6):3–9.
[15] Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010;11:781–9.
[16] Morse DE, Kerr AR. Disparities in oral and pharyngeal cancer incidence, mortality and survival among black and white Americans. J Am Dent Assoc 2006;137:203–12.
[17] National Conference of State legislatures. HPV vaccine: state legislation and statutes. http://www.ncsl.org/issues-research/health/hpv-vaccine-state-legislation-and-statutes.aspx [accessed 15.11.12].
[18] Harris V, Jackson RS, Ward M, Cardarelli KM, Kurian A, Raines A, et al. The HPV vaccine: a look at both sides of the debate. www.centerforcommunityhealth.org/. . ./HPVBriefFinal-NoBlank.pdf [accessed 17.11.12].
[19] Reiter PL, Stubbs B, Panozzo CA, Whitesell D, Brewer NT. HPV and HPV vaccine education intervention: effects on parents, healthcare staff, and school staff. Cancer Epidemiol Biomarkers Prev 2011;20:2354–61.
[20] Davis K, Dickman ED, Ferris D, Dias JK. Human papillomavirus vaccine acceptability among parents of 10- to 15-year-old adolescents. J Low Genit Tract Dis 2004;8:188–94.
[21] Wetzel C, Tissot A, Kollar LM, Hillard PA, Stone R, Kahn JA. Development of an HPV educational protocol for adolescents. J Pediatr Adolesc Gynecol 2007;20:281–7.
[22] Beatty BG, O'Connell M, Ashikaga T, Cooper K. Human papillomavirus (HPV) education in middle and high schools of Vermont. J Sch Health 2003;73:253–7.
[23] Friedman AL, Shepeard H. Exploring the knowledge, attitudes, beliefs, and communication preferences of the general public regarding HPV: findings from CDC focus group research and implications for practice. Health Educ Behav 2007;34:471–85.
[24] Kirby D. Comprehensive school health and the larger community: issues and a possible scenario. J School Health 1990;60:170–7.
[25] Lefkowitz ES, Romo LF, Corona R, Au TK, Sigman M. How Latino American and European American adolescents discuss conflicts, sexuality, and AIDS with their mothers. Dev Psychol 2000;36:315–25.
[26] Akers AY, Holland CL, Bost J. Interventions to improve parental communication about sex: a systematic review. Pediatrics 2011;127:494–510.

[27] Pluhar EI, Kuriloff P. What really matters in family communication about sexuality? A qualitative analysis of affect and style among African American mothers and adolescent daughters. Sex Educ 2004;4:303–21.
[28] Marsman JC, Herold ES. Attitudes toward sex education and values in sex education. Fam Relat 1986;35:357–61.
[29] Burgess V, Dziegielewski SF, Green CE. Improving comfort about sex communication between parents and their adolescents: practice-based research within a teen sexuality group. Brief Treat Crisis Interv 2005;5:379–90.
[30] Constantine NA, Jerman P, Huang AX. California parents' preferences and beliefs regarding school-based sex education policy. Perspect Sex Reprod Health 2007;39:167–75.
[31] Eaton DK, Kann L, Kinchen S, Shanklin S, Flint KH, Hawkins J, et al. Youth risk behavior surveillance-United States. MMWR Surveill Summ 2012 2011;61:1–162.
[32] Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European guidelines for quality assurance in cervical cancer screening—summary document. Ann Oncol 2010;21:448–58.
[33] Akers AY, Newmann SJ, Smith JS. Factors underlying disparities in cervical cancer incidence, screening, and treatment in the United States. Curr Probl Cancer 2007;31:157–81.
[34] Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol 2008;44:10–22.
[35] Giuliano AR, Palefsky JM, Goldstone S, Moreira Jr ED, Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med 2011;364:401–11.
[36] Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer 2008;113(Suppl. 10):3036–46.
[37] Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS ONE 2013;8:e68329.
[38] Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007;57:7–28.
[39] Ohri LK. HPV vaccine: immersed in controversy. Ann Pharmacother 2007;41:1899–902.
[40] Schwartz J, Caplan A, Faden R, Sugarman J. Lessons from the failure of human papillomavirus vaccine state requirements. Clin Pharmacol Ther 2007;82:760–3.
[41] Balog JE. The moral justification for a compulsory human papillomavirus vaccination program. Am J Public Health 2009;99:616–22.
[42] Stern AM, Markel H. The history of vaccines and immunization: familiar patterns, new challenges. Health Aff 2005;24:611–21.
[43] Orenstein WA, Hinman AR. The immunization system in the United States—the role of school immunization laws. Vaccine 1999;17(Suppl. 3):S19–24.
[44] Malone KM, Hinman AR. Vaccination mandates: the public health imperative and individual rights. In: Goodman RA, Rothstein MA, Hoffman RE, et al., editors. Law in public health practice. New York, NY: Oxford University Press; 2003. p. 262–84.
[45] Dempsey AF, Mendez D. Examining future adolescent human papillomavirus vaccine uptake, with and without a school mandate. J Adolesc Health 2010;47:242–8, e246.
[46] Arbyn M, de Sanjosé S, Saraiya M, Sideri M, Palefsky J, Lacey C, et al. EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. Int J Cancer 2012;131:1969–82.
[47] Donovan B, Franklin N, Guy R, Grulich AE, Regan DG, Ali H, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. Lancet Infect Dis 2011;11:39–44.
[48] Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011;377:2085–92.
[49] Bosch FX, de Sanjose S, Castellsague X. The prospects of HPV vaccination in cervical cancer prevention: results of a new independent trial. Cancer Discov 2011;1:377–80.
[50] Binagwaho A, Wagner CM, Gatera M, Karema C, Nutt CT, Ngabo F. Achieving high coverage in Rwanda's national human papillomavirus vaccination programme. Bull World Health Org 2012;90:623–8.
[51] Gostin LO, DeAngelis CD. Mandatory HPV vaccination. JAMA 2007;297:1921–3.
[52] Stewart A. Childhood vaccine and school entry laws: the case of HPV vaccine. Public Health Rep 2008;123:801.
[53] Recommendations on the use of quadrivalent Human Papillomavirus Vaccine in males—Advisory Committee on Immunization Practices (ACIP); 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm [accessed 15.11.12].
[54] Giuliano AR, Anic G, Nyitray AG. Epidemiology and pathology of HPV disease in males. Gynecol Oncol 2010;117(Suppl. 2):15–9.
[55] Centers for Disease Control and Prevention. HPV and men-fact sheet. Available at http://www.cdc.gov/std/hpv/stdfact-hpv-and-men.htm [accessed 27.04.13].
[56] Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. Cancer 2004;101:281–8.
[57] Vamos CA, McDermott RJ, Daley EM. The HPV vaccine: framing the arguments FOR and AGAINST mandatory vaccination of all middle school girls. J Sch Health 2008;78:302–9.
[58] Gerend MA, Barley J. Human papillomavirus vaccine acceptability among young adult men. Sex Transm Dis 2009;36:58–62.
[59] Giuliano AR. Human papillomavirus vaccination in males. Gynecol Oncol 2007;107:24–6.
[60] Ault KA. Human papillomavirus vaccines and the potential for cross-protection between related HPV types. Gynecol Oncol 2007;107:31–3.
[61] Centers for Disease Control and Prevention (CDC). Ten great public health achievements-United States, 1900–1999. MMWR Morb Mortal Wkly Rep 1999;48:241–8.
[62] Salmon DA, Teret SP, MacIntyre CR, Salisbury D, Burgess MA, Halsey NA. Compulsory vaccination and conscientious or philosophical exemptions: past, present, and future. Lancet 2006;367:436–42.
[63] Albert MR, Ostheimer KG, Breman JG. The last smallpox epidemic in Boston and the vaccination controversy, 1901–1903. N Engl J Med 2001;344:375–9.
[64] Gross CP, Sepkowitz KA. The myth of the medical breakthrough: smallpox, vaccination, and Jenner reconsidered. Int J Infect Dis 1998;3:54–60.
[65] Mercer AJ. Smallpox and epidemiological-demographic change in Europe: the role of vaccination. Popul Stud (Camb) 1985;39:287–307.
[66] Bonanni P. Demographic impact of vaccination: a review. Vaccine 1999;17:120–5.
[67] Ritvo P, Wilson K, Willms D, Upshur R, Goldman A, Kelvin D, et al. Vaccines in the public eye. Nat Med 2005;11:20–4.
[68] Zimmerman RK. Ethical analysis of HPV vaccine policy options. Vaccine 2006;24:4812–20.
[69] Osazuwa-Peters N. Determinants of health disparities: the perennial struggle against polio in Nigeria. Int J Prev Med 2011;2:117–21.
[70] Hu D, Goldie S. The economic burden of noncervical human papillomavirus disease in the United States. Am J Obstet Gynecol 2008;198:500e1–7.
[71] The value of HPV vaccination. Nat Med 2012;18:28–9.
[72] Palefsky JM. Human papillomavirus-related disease in men: not just a women's issue. J Adolesc Health 2010;46:12–9.
[73] Villa LL. Prophylactic HPV vaccines: reducing the burden of HPV-related diseases. Vaccine 2006;24:23–8.
[74] Daley MF, Liddon N, Crane LA, Beaty BL, Barrow J, Babbel C, et al. A national survey of pediatrician knowledge and attitudes regarding human papillomavirus vaccination. Pediatrics 2006;118:2280–9.
[75] Dempsey AF, Davis MM. Overcoming barriers to adherence to HPV vaccination recommendations. Am J Manag Care 2006;12(Suppl. 17):484–91.
[76] Fang CY, Coups EJ, Heckman CJ. Behavioral correlates of HPV vaccine acceptability in the 2007 Health Information National Trends Survey (HINTS). Cancer Epidemiol Biomarkers Prev 2010;19:319–26.
[77] Haug C. The risks and benefits of HPV vaccination. JAMA 2009;302:795–6.
[78] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009;302:750–7.
[79] Colgrove J. The ethics and politics of compulsory HPV vaccination. N Engl J Med 2006;355:2389–91.
[80] Ciolli A. Mandatory school vaccinations: the role of tort law. Yale J Biol Med 2008;81:129–37.
[81] Tomljenovic L, Shaw CA. Too fast or not too fast: the FDA's approval of Merck's HPV vaccine Gardasil. J Med Ethics 2012;40:673–81.
[82] National Center for Immunization and Respiratory Disease. Vaccines and preventable diseases: HPV vaccine – questions & answers. http://www.cdc.gov/vaccines/vpd-vac/hpv/vac-faqs.htm [accessed 27.03.13].
[83] U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. Healthy People 2020. www.healthypeople.gov/2020/. . ./objectiveslist.aspx?topicid=32 [accessed 21.03.12].