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Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference

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ABSTRACT

In Italy, the cohorts of women who were offered Human papillomavirus (HPV) vaccination in 2007/08 will reach the age (25 years) for cervical cancer (CC) screening from 2017. The simultaneous shift from cytology-based screening to HPV test-based screening gives the opportunity for unprecedented reorganisation of CC prevention. The ONS (National Screening Monitoring Centre) Directive and the GISCi (Italian Group for Cervical Screening) identified the consensus conference as the most suitable method for addressing this topic. A summary of consensus recommendations is reported here. The main objective was to define the best screening methods in girls vaccinated against HPV and the knowledge required for defining evidence-based screening strategies. A Jury made recommendations about questions and proposals formulated by a panel of experts representative of Italian scientific societies involved in CC prevention and based on systematic reviews of literature and evidence. The Jury considered changing the screening protocols for girls vaccinated in their twelfth year as appropriate. Tailored screening protocols based on vaccination status could be replaced by "one size fits all" protocols only when a herd immunity effect has been reached. Vaccinated women should start screening at age 30, instead of 25, with HPV test. Furthermore, there is a strong rationale for applying longer intervals for re-screening HPV negative women than the currently recommended 5 years, but research is needed to determine the optimal screening time points. For non-vaccinated women and for women vaccinated in their fifteenth year or later, the current protocol should be kept.

Abbreviations: AIRTUM, Italian Association of Cancer Registries; AOGOI, Italian hospital obstetric gynaecologists Association; CC, cervical cancer; CI, Confidence Interval; CIN, Cervical Intraepithelial Neoplasia; DNA, Deoxyribonucleic acid; GISCi, Italian Group for Cervical Screening; hr HPV, high-risk Human Papillomavirus; HTA, Health Technology Assessment; IARC, International Agency for Research on Cancer; ICO, Catalan Institute of Oncology; ISTAT, The Italian National Institute of Statistics; IT, information technology; ONS, National Screening Monitoring Centre; PASSI, "Progressi dell'Aziende Sanitarie per la Salute in Italia" survey; PC, Promoter Committee; RR, Relative Risk; SIAPEC, Italian Society of Pathology and Diagnostic Cytology; SICi, Italian Society of Cytology; SICPCV, Italian Society of Colposcopy and Cervico-Vaginal Pathology; SIGO, Italian Society of Gynecology and Obstetrics; SItI, Italian Society of Hygiene, Preventive medicine and Public Health; TSC, Technical and Scientific Committee.

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1. Introduction

In Italy, in the near future the cohorts of women who were offered Human papillomavirus (HPV) vaccination will be reaching the age for screening for the precursors of invasive cervical cancer (ICC). This happens while screening is moving from being cytology-based to HPV-based. This situation represents a challenge but also an opportunity for unprecedented reorganisation of CC prevention (WHO/RHR, 2006).

In Italy, organised vaccination and cervical screening are managed by Regions, according to national prevention and vaccination plans. Current national screening guidelines recommend invitation for cytology-based screening every 3 years from age 25 to 30–35 years and for HPV-based screening every 5 years thereafter up to age 64. According to the national vaccination strategy, girls are invited for HPV vaccination during their 12th year of age. This strategy started in 2008, inviting the cohort of women born in 1996, who will reach 25 years - the age for being invited for screening - in 2021. In addition, some Regions adopted a multi-cohort vaccination strategy, vaccinating adolescents in their 16th or 18th year. The first of them are reaching 25 years in 2016, most will in 2018 (Giambi, 2014). Further details on the implementation of both programs are provided in Results (Question 1).

This new situation means that organised screening programs must review their strategies. In this context, providing regional decision makers (as it happened for HPV-based screening) with clear, practical and feasible national information, based on the best scientific evidence and defined with the participation of professional involved in the subject, is fundamental in order to standardise procedures throughout the country. Indeed, concerning HPV-based screening, a Health Technology Assessment report was published in 2012 on the basis of a systematic literature review about efficacy and undesired effects, conducted also in the frame of the preparation of EU guidelines (Ronco et al., 2012). It advised moving to HPV-based screening- and provided a detailed protocol. The national Ministry of Health (MOH) endorsed such conclusions in 2013. After direct evidence of greater efficacy of HPV-based screening in preventing ICC, (Ronco et al., 2014) the 2014 National Prevention Plan required a progressive shift to HPV-based screening within 2018 (AIRTUM, 2015).

A Consensus Conference was organised in 2015. Its main objective was to define the best screening methods in girls vaccinated against HPV and the knowledge required for defining evidence-based screening strategies. The Consensus Conference identified and defined the central and local actions to be implemented in order to optimise the integration of primary prevention programs with secondary prevention programs, as well as research activities connected with the knowledge needed for change.

A summary is reported here (Fig. 1).

2. Materials and methods

2.1. Consensus Conference organisation

The ONS (National Screening Monitoring Centre, a governmental agency supporting the MOH and local health authorities in screening implementation and monitoring) Directive and the GISCi (Italian Group for Cervical Screening, the scientific society of Italian organised cervical screening programmes) Coordination Committee defined the general aim and identified a Promoter Committee.

The Promoter Committee, including four technical experts from ONS and GISCi, identified the Consensus Conference model (Supplementary Figure), developed by the national system for guidelines (http://www.snlg-iss.it/), as the most suitable method. The Promoter Committee appointed a Scientific Committee (SC), including experts, and a Jury, including experts and stakeholders.

The Technical Scientific Committee defined the objective and scope. Then it collected and summarised available evidence. Work packages were assigned to TSC members or to external experts, identified by their recent research. A pre-conference document with questions (see Table 1), proposed solutions (see Table 2) and the evidence supporting the proposed solutions was prepared.

For each question the Jury expressed an answer, which could be:

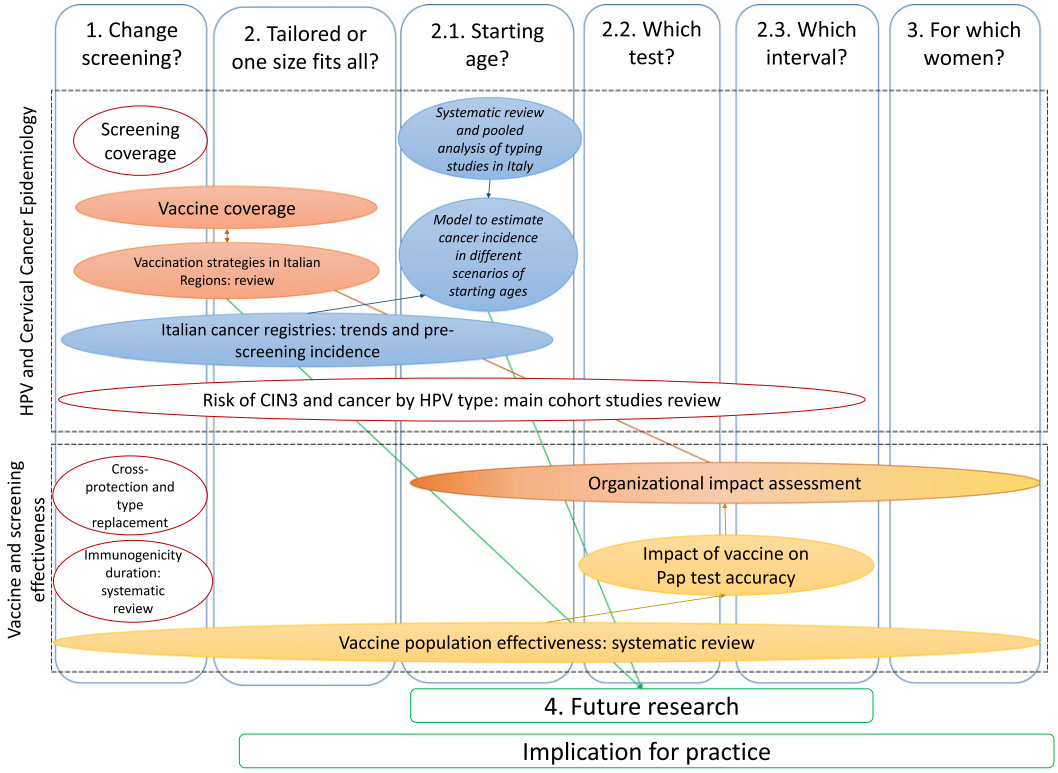

Fig. 1. Contribution of the work packages to the evidence supporting screening recommendations for the individual questions posed.

○ Consensus for the recommendation;
○ Consensus for the recommendation but need for reformulation, providing relevant indications;
○ No consensus for the recommendation.

The Italian integral report is published on the ONS (www.osservatorionazionalescreening.it) and GISCi (www.gisci.it) websites, and has been officially presented to decision makers: the Ministry of Health and the State-Regions Conference. Here we present an English summary.

2.2. Evidence retrieval

2.2.1. Epidemiological overview

From the ITACAN database, the current Invasive Cervical Cancer (ICC) incidence rates in Italy by calendar period (before and after organised screening implementation) and by age (<25 years – age of screening start, 25–29 and 30–35 years) were calculated (AIRTUM, 2015). An analysis of vaccination strategies in each region was performed (Intesa tra il Governo le Regioni e le Provincie autonome, 2007). Vaccination coverage with 1, 2 and 3 doses, by region and birth cohort was retrieved (Giambi, 2014; Giambi et al., 2013; Intesa tra il Governo, le Regioni e le Province autonome di Trento e Bolzano, 2015). Screening coverage by region and age was obtained from ONS surveys (ONS, 2015).

2.2.2. Risk of CIN3 and cancer by HPV type: main cohort studies review

A non-systematic review of the incidence of CIN3 or more severe lesions (CIN3 +) in women positive for individual high-risk HPV (hrHPV) types was conducted. Four cohorts about whom data of good methodological quality were published during the past 10 years were identified (Khan et al., 2005; Castle et al., 2009; Kjær et al., 2010; Schiffman et al., 2011; Thomsen et al., 2015). The outcome considered was the cumulative incidence of CIN3 + at 3–5 and 10–16 years, in women positive for HPV16, HPV18 and non-16/18 hrHPV.

2.2.3. Systematic review and pooled analysis of typing studies in Italy

The systematic review performed by the ICO HPV Information Centre, updated to 30 June 2014, was considered as methodologically sound (Bruni et al., 2015). Starting from it 14 studies reporting ICC genotyping in Italy were selected (Bruni et al., 2015). Only 3 of them had published data on the proportion of types HPV 16/18 by age and year of diagnosis (Giorgi Rossi et al., 2012a). The authors of the remaining studies were contacted and 8 of them provided data, including molecular method used, histological type, presence of HPV DNA, identified types, year of diagnosis, age at diagnosis and province of residence. The proportion of non-HPV16/18 cancers in women aged <30 years before organised screening started was estimated by pooling all retrieved data. Each cancer was classified as occurring before organised screening if at the date of incidence <50% of the target population in its area of residence (province) had been invited by the local organised screening

Table 1
Questions posed by the Scientific Technical Committee to the Jury.

Consensus Conference questions
1. Do the protocols for screening programs need to be changed upon the arrival of the cohorts of vaccinated women?
2. If so, which policy appears to be the most effectively and operatively manageable?
o A tailored strategy;
o A one size fits all strategy.
2.1. At what age should screening start?
2.2. With which test?
2.3. How often?
3. Should the strategy be different for the cohorts vaccinated in their 15th year (or later) with respect to those vaccinated in their 12th year?
4. Which actions need to be scheduled from now and up to 2021 in order to acquire missing evidence and to make the integration of primary and secondary prevention practically possible?

Table 2
Synthesis of the recommendations proposed by the Scientific Technical Committee and Jury's response to the first 3 questions posed at the Consensus Conference.

Q.	Proposals of the Scientific Technical Committee	Recommendations of the Jury
1	Based on international literature, the participants in the Consensus Conference consider changing the screening program protocols upon the arrival of the vaccinated cohorts as appropriate.	The Jury responded positively with full consent. Tailored screening protocols based on the vaccination status could at some point be replaced by one size fits all screening protocols, when the vaccination coverage has reached levels such that infections from HPV16/18 (included in the vaccines currently used) can be considered practically negligible. The Jury also stressed the fact that screening activity must continue and be performed within organised screening programs also for vaccinated women.
2	For girls vaccinated in their 12th year, i.e. presumably naive, a combined sequential strategy is proposed: 1. Tailored strategy 2. One size fits all strategy: this method may be adopted when local coverage reaches the threshold established by the Ministry for vaccination coverage.	The Jury approves with full consent the proposal that invites the Regions to link as soon as possible individual data between lists of vaccinated women and lists of women invited to and/or who participated in screening, in accordance with data protection regulations. The Jury also recommends that tailored protocols, according to vaccination status, are gradually extended to all Italian Regions, in parallel with the implementation and validation (for quality and completeness) of IT systems. The Jury agrees to consider a uniform strategy as the final objective of the process, believing that the minimum level of vaccination coverage must be carefully assessed. This, according to the Jury, could be well below 95%.
2.1	There is a strong rational for proposing an increase in the starting age for screening to 30 years for girls vaccinated in their twelfth year.	For girls vaccinated in their 12th year (±1 year), the Jury accepts, with full consent, the proposal to increase the starting age for screening to 30 years.
2.2	In girls vaccinated in their12th year, the screening test will be the HPV test. In the cohorts vaccinated in their 15th year or later (screening starting at age 25) Pap testing will initially remain.	The Jury accepts with full consent the choice of the HPV test as the screening test for women vaccinated in their 12th year (suggesting screening start at age 30). For non-vaccinated women, in agreement with a tailored strategy, the current protocol must be continued, with cytological screening in the 25–29 age range and HPV test with cytology triage from age 30 to 64.
2.3	Currently there is no evidence on the optimal intervals between rounds, although there is a strong rational that intervals should be longer. To estimate ideal intervals, the data that the screening data in girls vaccinated in their 15th year of age or later will be fundamental.	The Jury recognises the lack of evidence on the optimal interval between screening rounds in vaccinated women, while acknowledging the strong rational in favour of a longer interval than 5 years, i.e. the interval currently recommended for the HPV test in the female population in general. It also adheres with full consent to the proposal to promptly start studies on this subject.
3	Changes in screening protocols are to be applied only to the cohorts of girls vaccinated in their 12th year.	The Jury is favourable, with full consent, to the recommendation not to change current cytological screening protocols for women vaccinated in their 15th year or later.

program (Serraino et al., 2015). This classification does not consider opportunistic activity, which in some areas was already very widespread prior to organised programs.

2.2.4. Model to estimate cancer incidence in different scenarios of screening starting ages

In order to estimate the impact of increasing the starting age for screening in vaccinated women, we estimated the incidence of non-HPV16/18 cancers before the start of organised screening (1990–1998) in women aged <25, <30 and <35 years (Fig. 2). Three different estimates of the proportion of non-HPV16/18 ICC were obtained by a pooled analysis of Italian ICC genotyping studies: a) the raw observed proportion; b) an estimate based on a model including age with linear effect and presence/absence of organised screening; c) an estimate based on a model including age as categorical variable (≤29, 30–34, ≥35) and presence/absence of organised screening. Such proportions were applied to ICC incidences before organised screening implementation in Italy (i.e. in the 1990s) and the resulting incidences to the 2015 Italian population. The overall ICC incidence in the same period below age 25, the starting age for invitation to screening according to the Italian 1996 recommendations was also computed (Commissione Oncologica Nazionale, 1996). That incidence applied to the 2015 Italian population would give 8 cases per year, which were used as reference threshold.

2.2.5. Immunogenicity duration: systematic review

A systematic review of the literature on immunogenicity and effectiveness of the vaccines against HPV was performed (Brown et al., 2006). The target population was represented by women aged between 19 and 44 years. The outcomes considered were: infection from hrHPV, persistent infection (≥6 months or ≥12 months) with hrHPV, onset of persistent lesions, CIN1 +, cytological abnormalities (ASC-US or more severe) and antibody levels IgG and/or neutralising antibodies against HPV16 and HPV18. Studies measuring outcomes at 5 years or more after vaccination were included.

2.2.6. Cross-protection and type replacement

A non-systematic review of dynamic models on the natural history of cervical cancer and the effect of the vaccine was performed. A narrative summary of the results of models on cross-protection and type replacement was prepared.

2.2.7. Population effectiveness of the vaccine: systematic review

A systematic review of the literature on the effectiveness of vaccination in practice at population level was performed. The outcomes considered were: infection occurrence, cytological results, incidence or detection rate of CIN2, CIN3, and ICC. Genital warts were considered as indirect evidence for possible herd immunity effect. The review started from the work of Drolet et al. (Drolet et al., 2015), updating the research up to 8 September 2015 (Drolet et al., 2015).

2.2.8. Impact of vaccine on Pap test accuracy

A non-systematic review of literature about the impact of vaccination on the accuracy of screening tests and on the performance of screening was performed. Its results were read in the light of the results of the systematic review on the effectiveness of the vaccine at population level.

2.2.9. Organizational impact assessment

Based on the HTA report on primary screening with HPV, the consequences of vaccination and possible changes of the screening protocol on the organisation of health services were hypothesised. Particular attention was given to the centralisation of laboratories and the linkage between vaccination records and screening management systems (Ronco et al., 2012). For this latter point, a feasibility analysis was performed on the system put in place in the Lazio Region for connecting the two databases.

3. Results and discussion

The recommendations proposed by the Scientific Technical Committee and Jury's responses are reported at Tables 2 and 3. The results of

Estimating the incidence of cancer non-HPV16/18 in absence of screening.

Age	Incidence*10^{-5}	No.
<25	0.093	8.0
<30	0.493	51.1
<35	1.531	191.4

Data from AIRTUM database years 1990-98

Age	Proportion of non16-18 HPV		
	Raw	Model A	Model B
<25	10%	15%	20%
<30	10%	15%	21%
<35	10%	11%	22%

Data from pooled analysis of Italian typing studies. Model A includes age in classes (<30; 30-34; >=35), presence of organised screening and typing laboratory; Model B includes age with linear effect, presence of organised screening and typing laboratory.

Age	Italian female population 2015
<25	8,578,416
<30	10,375,465
<35	12,500,727

Data from ISTAT, 31/12/2014

Estimating the Number of non-preventable cancers in the Italian population 2015 when starting screening at different ages.

Age	Estimated Number of non-preventable cancers		
	Raw	Model A	Model B
<25	0.8	1.3	1.6
<30	5.0	5.5	10.5
<35	19.1	49.1	42.9

Fig. 2. Estimation of invasive cervical cancer incidence nationwide in different scenarios of starting ages. (Italy; 2015).

evidence retrieval and relevant background information about Italy are reported hereafter.

3.1 Question 1. - Do the protocols for screening programs need to be changed upon the arrival of the cohorts of vaccinated women?

3.1.1. Screening coverage

Organised population-based cervical screening started in Italy in the 1990ies, following widespread opportunistic activity. Their introduction was followed by a significant reduction of ICC in the corresponding areas (AIRTUM, 2015; Serraino et al., 2015; Giorgi Rossi et al., 2015). Reports based on standardized process indicators are published yearly. In 2013 70% of Italian women aged 25 to 64 years (3,693,165 women) received a letter inviting them to take part in the local cervical screening program and 41.5% accepted (ONS, 2015).

HPV-based screening has been recommended since 2013. Women aged 30–35 (based on regional choice) to 64 years are invited every 5 years to testing for the DNA of high-risk HPV types by validated test as stand-alone primary test. HPV-negative women will be re-invited in 5 years. HPV-positive women are tested by reflex cytology and referred to colposcopy if it is ASC-US or more. If cytology is normal women are re-invited for new HPV testing after 12 months and referred to colposcopy if still positive. If the new HPV test is negative they are re-invited for a new screening round in 5 years.

The introduction of HPV-based screening in routine activity is starting at different times in different regions. In addition, in order to avoid too large variations in workload due to the interval change, all regions invite an increasing proportion of eligible women for HPV, reaching 100% not before 3 years. In 2015 HPV-based screening was proposed to 16.0% of the women invited for cervical screening in Italy. Some 50.1% of them accepted (www.osservatorionazionalescreening.it).

In addition to the organised programs, there is spontaneous screening. The national survey PASSI reports that, during the 2011–14 period, 78.7% of women aged 25 to 64 years reported having undergone a Pap test (or an HPV test) during the past 3 years. Slightly more than half stated they had done this in public facilities, free of charge within screening programs. This proportion had increased since active surveillance began (in 2008) (CNESPS and ISS, 2015a). There are however marked differences in invitational coverage, participation and opportunistic activity between Italian regions (ONS, 2015; CNESPS and ISS, 2015a).

3.1.2. Risk of CIN3 and cancer by HPV type: main cohort studies review

The non-systematic review of the 4 cohorts showed that, for women with infection by HPV16, the risk of CIN3 + is 2.1 to 8.1 fold that of women with infections by non-16/18 HPV types (Khan et al., 2005; Castle et al., 2009; Kjær et al., 2010; Schiffman et al., 2011; Thomsen et al., 2015). The risk for women with infection by HPV18 is 1 to 4.4 fold that of women with infection by non-16/18 HPV types. Infection from HPV16 or HPV18 or HPV45 is associated with a younger median age at onset, resulting in a higher proportion of HPV16/18- positive cancers among younger women (Giorgi Rossi et al., 2012a; de Sanjose et al., 2010; Carozzi et al., 2010; de Sanjose et al., 2011).

3.1.3. Immunogenicity duration: systematic review

The systematic review, based on 13 studies, concluded that, for the bivalent vaccine, immunogenicity and protection against infections and CIN2 + attributable to HPV16 or 18 lasted at least 9.4 years (Villa et al., 2006; Olsson et al., 2007; Harper, 2008; GlaxoSmithKline Vaccine HPV-007 Study Group et al., 2009; De Carvalho et al., 2010; Lu et al., 2011; Romanowski, 2011; Roteli-Martins et al., 2012; Luna et al., 2013; Naud et al., 2014; Ferris et al., 2014; Deleré et al., 2014; Schwarz et al., 2015).

For the quadrivalent vaccine a follow up of 8 years was available, during which a sustained antibody response to HPV16 was proven (Ferris et al., 2014). Over the same period, the GMT titer for HPV 18 was 27 to 34 fold lower than the one reached at the 7th month, with a plateau from the 18th to the 72nd month. It is not possible to define the efficacy due to lack of an 8-year control group. Anyway, no HPV 6/11/16/18 related lesion nor infection persisting for ≥12 months was reported in the women vaccinated at the beginning of the study.

Table 3
Recommendations proposed by the Scientific Technical Committee and the Jury's response to the fourth question.

Proposal of the scientific technical committee approved and integrated by the jury
Recommendations for implementation

a) Link between vaccination records and screening registers. The computerisation of vaccination records and the construction of archives at regional and national level that are connected reciprocally and with other databases is among the objectives of the 2014–2018 National Prevention Plan (Objective 9.6). The link should take place at least at regional level because girls could move around, hence changing local health administration from where the vaccination takes place in their 12th year to where the first invitation for screening at age 25 or 30 occurs.
b) Definition of a minimum set of information that the vaccination registers must make available for screening programs;
c) Timeline definition of points a) and b);
d) Introduction of recording of CIN2 + in cancer registers and link between vaccination registers and cancer registers; the jury recommends improving cancer registration by recording diagnostic-therapeutic data;
e) Analysis of participation, referral for colposcopy and detection rate of high grade CIN and ICC in screening programs for vaccinated and non-vaccinated women;
f) Inclusion in screening archives (until vaccination record integration) of the following data as reported by women:
i. Vaccination against HPV performed (yes/no);
ii. Number of doses;
iii. Vaccine type;
iv. Vaccination date for each dose;

Finally the Jury recommends:
Given the substantial change in screening practices, a substantial effort should be dedicated to training healthcare operators, so that they can provide to the general population useful and scientifically correct information on the changes to screening practices, their efficacy, the type of test used and the starting age.

Research recommendations
g) Studies to perform:

i. Promote the conduction of studies, with a protocol shared at national level, in order to identify conservative protocols that allow the use of the HPV testing in women aged 25–29 years;
ii. Enrol a large cohort of vaccinated women who are HPV negative at screening. Their detection rate of CIN3 + should be determined at subsequent screens. In particular, for the cohorts of girls vaccinated in their 15th/16th year, if their infection status for HPV is determined at their first screen (from 2016), such study design can be applied for measuring the subsequent CIN3 + reduction and defining optimal screening intervals (Fig. 3);
iii. Promote studies on the level of association between participation to screening and to vaccination (or women's decision to vaccinate their daughters);
iv. Promote studies to assess whether the new nonavalent vaccine could change the fundamental elements of the decision-making tree presented herein;
v. Qualitative investigations to identify tools and methods for communicating the screening change to women and operators.

Finally the Jury recommends:
assessing the offer, the acceptance and the efficacy of the anti-HPV vaccination in women not previously vaccinated at the start of the screening programs at age 35.

3.1.4. Vaccine population effectiveness: systematic review

The 20 studies selected in the review by Drolet et al. report follow up data for >140 million person-years (Drolet et al., 2015; Tabrizi et al., 2012; Australian Institute of Health and Welfare, 2013; Sandø et al., 2014; Chow et al., 2015; Brotherton et al., 2015). In countries where a vaccination coverage ≥50% was reached in girls aged 13 to 19 years, infections by HPV 16/18 were 68% (RR 0.32, 95%CI 0.19–0.52) lower after vaccination than before. A lower reduction of infections by HPV 31, 33 and 45 (RR 0.72 95%CI 0.54–0.96) was observed, which suggests cross-protection. A significant drop in anogenital warts was also observed in adolescents below age 20 (RR 0.66 95%CI 0.47–0.91) and in women aged 20–39 years (RR 0.68 95%CI 0.51–0.89). This suggests a

substantial herd immunity effect. In countries where the vaccination coverage was <50% significant reductions in infections from HPV 16/18 (RR 0.50 95%CI 0.34–0.74) have been observed in girls under the age of 20, without any evidence of cross-protection or herd effect.

More recent studies confirm the effectiveness of vaccines (Kavanagh et al., 2014; Pollock et al., 2014; Baldur-Felskov et al., 2014). Pollock et al. observed a reduction in CIN1 (RR 0.71, 95%CI 0.58–0.87; p = 0.0008), CIN2 (RR 0.5, 95%CI 0.40–0.63; p = 0.0001) and CIN3 (RR 0.45, 95%CI 0.35–0.58; p = 0.0001) in vaccinated women aged 20–21 compared to those who had not been vaccinated. Baldur-Felskov et al. observed a 33.4% reduction of positive cytologies among girls aged <18 years and 12.6% among girls aged 18–20 years (Pollock et al., 2014; Baldur-Felskov et al., 2014).

3.1.5. Cross-protection and type replacement

Some cross-protection by bivalent and quadrivalent vaccines towards different non-16/18 HPV genotypes emerged from the systematic review on effectiveness. There is not yet sufficient evidence on the duration of such protection (Lipsitch, 1999; Palmroth et al., 2012; Lehtinen and Dillner, 2013; Joura et al., 2015; Kreimer et al., 2015).

The concept of type replacement denotes two different phenomena, one related to competition for the ecological niche and one connected with the presence of competitive risks. If there was ecological competition between different HPV genotypes, the long-term effectiveness of the vaccination would be reduced due to the increase in infections by non-16/18 types. This phenomenon would imply a negative association between infections with different genotypes, a phenomenon that was never observed in many cross-sectional studies (Carozzi et al., 2010). As for competitive risks, it is actually plausible that, in case of co-presence of lesions due to different genotypes, those that progress more rapidly to invasive cancer (like those due to HPV16/18) may prevent the onset of cancers due to the other genotype(s) infections. This can happen either because during treatment the lesion which has not yet progressed is also removed or, less frequently, because the first cancer causes death before the second lesion progresses to invasion. It is therefore reasonable to expect that in a vaccinated population the occurrence of lesions and cancers attributable to non-vaccine HPV will increase.

3.2 Question 2. - If so, which policy appears to be the most effectively and operatively manageable? Tailored or one size fits all?

3.2.1. Vaccine coverage in Italy

In Italy vaccine coverage does not reach the 95% objective, which is traditionally used for vaccine coverage for common childhood diseases, such as measles. The national coverage in cohorts of 12-year-old girls is 71%, with regions that do not reach 50% (Giambi, 2014; Giambi et al., 2013; Intesa tra il Governo, le Regioni e le Province autonome di Trento e Bolzano, 2015). The recommended schedule is currently 2 doses for the 12 years old girls (Dobson et al., 2013; CSS, 2015).

3.2.2. Vaccination strategies in Italy

Vaccination was extended to cohorts of 16-, 18- or 25-year old women only in some regions. Coverage was lower than in 12-year old girls (Intesa tra il Governo le Regioni e le Provincie autonome. Strategie per l'offerta attiva del vaccino contro l'infezione da HPV in Italia, 2007; CNESPS, ISS, 2015b). These coverage levels are borderline for resulting in a herd immunity effect, i.e. in a reduction of infection and cancer risk among unvaccinated women (Drolet et al., 2015).

3.2.3. Italian cancer registries: trends and pre-screening incidence

AIRTUM, the association of Italian cancer registries, estimated 2135 new invasive cervical cancers nationwide during 2014. Of them 35 are expected in the 25–29 age range and 125 in the 20–34 age range (AIRTUM, 2015). Before organised screening (1990 to 1998), there were 190 cases between 20 and 34 years of age (Fig. 2).

Between 2006 and 2009, 5 deaths from cervical cancer were recorded in women aged 20 to 34 years. Time trends of ICC incidence rates show an increase, although ICCs remain very rare, in women below 30 years old. This is plausibly, related to increased occurrence of HPV infection in younger cohorts, because of changing sexual habits. In the 30–34 year age range the time trend is decreasing.

3.3 Question 2.1. - At what age should screening start?

3.3.1. Systematic review and pooled analysis of typing studies in Italy

The systematic reviews conducted by IARC show an increasing proportion of HPV16 and 18 with increasing grade of CIN and in ICC. The proportion of ICC attributable to HPV16 is higher in Europe than in some other continents (Clifford et al., 2003a; Clifford et al., 2003b; Smith et al., 2007; Guan et al., 2012; Guan et al., 2013). These results are in agreement with those of the review of cohort studies about progression times. It is less clear whether the proportion of HPV16 and 18 among all invasive cancers increases over time. This is because ICC time trends are compressed by increases in screening effectiveness and because of changing in typing accuracy (Li et al., 2011).

In the systematic review by ICO 25 Italian studies were included, 11 related to CIN3 and 14 to ICC, reaching a total of 2354 CIN3 and 1308 ICC genotyped (Bruni et al., 2015; Carozzi et al., 2010; Laconi et al., 2000; Zerbini et al., 2001; Tornesello et al., 2006; Gargiulo et al., 2007; Capra et al., 2008; Venturoli et al., 2008; Agarossi et al., 2009; Sandri et al., 2009; Giorgi Rossi et al., 2010; Spinillo et al., 2014; Garzetti et al., 1998; Voglino et al., 2000; Ciotti et al., 2006; Del Mistro et al., 2006; Lillo et al., 2008; Rolla et al., 2009; Sideri et al., 2009; Mariani et al., 2010; Tornesello et al., 2011).

The pooled analysis performed on 723 typed Italian ICC confirmed an increased frequency of HPV16 and 18 in younger women and increasing time trends, both for squamous cell carcinomas and for the other histological types (Carozzi et al., 2010; Tornesello et al., 2006; Gargiulo et al., 2007; Spinillo et al., 2014; Del Mistro et al., 2006; Lillo et al., 2008; Sideri et al., 2009; Mariani et al., 2010; Tornesello et al., 2011; Giorgi Rossi et al., 2012a).

3.3.2. Estimated cancer incidence under different scenarios of age to start

The number of cancers not prevented when increasing the age to start screening up to 30 years for vaccinated girls changed according to how the proportion of non-16/18 ICC was estimated ((a) raw, (b) from model with linear age effect or (c) from model with age in classes, see Methods). It was 5 ICC cases with approach (a), 10.5 ICC cases with approach (b) and 5.5 ICC cases with approach (c). By comparison, about 8 ICC cases cannot be prevented by screening programs each year nationwide because they occur at age < 25 (Commissione Oncologica Nazionale, 1996). When increasing the age of start of screening to 35 years un-prevented cancers would be 19 ICC cases with approach (a) 43 ICC cases with approach (b) and 49 ICC cases with approach (c).

3.4 Question 2.2. – With which test?

3.4.1. Impact of vaccine on Pap test accuracy

There is general agreement that in vaccinated women cytology will have a substantially lower positive predictive value (PPV) for CIN2+ than in the current situation. This will be due on one hand to the strong reduction in prevalence of CIN2+ among vaccinated women, depending on the lower prevalence of infections by high-risk HPV types and on the lower risk of progression to CIN2+ of infections from non-HPV16/18 genotypes (Giorgi Rossi et al., 2012b). On the other hand, false positive cytological abnormalities caused by low risk HPV infections or other conditions will still be present. Thus, the probability that cytological abnormalities correspond to a CIN2+, i.e. PPV, is expected to strongly decrease. The low prevalence of lesions could also reduce the ability of cytologists to recognize them, thus the sensitivity of cytology (Pollock et al., 2014; Franco et al., 2009; Tota et al., 2010). This is not

expected with cytology for triaging HPV, because the remaining CIN2+ will concentrate in HPV-positive women (Franco et al., 2009; Castle et al., 2011).

Were the age to start screening in Italy increased up to 30 years, then all women would be screened by HPV, which is already recommended in the general population from this age upwards (Ronco et al., 2012; von Karsa et al., 2015).

For the screening of a vaccinated population, it would also be appropriate to use tests that allow detecting the vaccine HPV types. This would also permit a more accurate assessment of the population effectiveness of vaccination. Affordable tests that combine the search for hrHPV types with HPV16 and HPV18 partial typing are already on the market.

With current guidelines, in Italy, non-vaccinated women would have cytology-based screening from 25 to 30/34 years of age and HPV-based screening thereafter.

3.5 Question 2.3. – With which interval?

To the moment there is a strong rational to state that screening intervals longer than the current ones will be safe in vaccinated women but there is not sufficient evidence to define their optimal length. In order to obtain early information the screening results at age 30 in the women vaccinated in their 16th year or later can be crucial. These women are not strictly comparable to those screened at 12 because of a greater probability of being already infected when vaccinated but those negative for HPV16 and 18 at age 25 either were not infected at vaccination or have cleared infection. In principle the ICC cumulative incidence after a negative test is the parameter of reference to define screening intervals. However, given the rarity of ICC, especially at young age, CIN3+ can be used as a surrogate, also because its prevalence is a strong determinant of screening efficiency. Thus, it can be chosen to apply a longer interval (e.g. 1 year) if the detection rate of CIN3+ at age 30 is lower than a reference value. This process can be repeated with further birth cohorts in order to accept longer intervals. In the NTCC trial, among women aged 25–34 years at enrolment, the detection of CIN3+ at the second screening round with cytology, after 3 years, was 1.5 per 1000. This represents the value implicitly accepted with cytology-based screening. A 1/1000 DR (33% lower) after a longer (≥5-years) interval can plausibly be considered as safe for moving to a 1-year longer interval.

Certainly, the residual disease threshold is age dependent and a threshold defined in young women cannot be extended to older women where the prevalence of CIN3 is lower but their risk of progression to cancer is higher. Therefore, as a safety check, vaccinated women screened with prolonged intervals will be followed-up and their detection rate compared to that observed in unvaccinated women of same age screened by HPV (see research recommendations and Fig. 3).

3.6 Question 3. - Should the strategy be diversified for the cohorts vaccinated in their fifteenth year (or later) with respect to those vaccinated in their twelfth year?

The vaccine strategies of regions have sometimes included additional cohorts of 16, 18 and 25-year old women. The Pregio study estimated a median age for first sexual intercourse in Italy of 17 years, without substantial differences between geographical areas (Donati et al., 2012). Therefore, it can be assumed that less than half of the girls vaccinated in their 16th year and more than half of those vaccinated subsequently have already had sexual intercourse and therefore may not be HPV-naive at vaccination. Vaccine is not effective on infection clearance (The FUTURE II Study Group, 2007; Paavonen et al., 2007).

At the same time, data on occurrence of infections and lesions in these cohorts collected by screening programs could be fundamental for filling the gaps in knowledge, providing useful elements for changing the screening program for girls vaccinated in their twelfth year. Thus, these cohorts should still be screened at age 25.

3.7. Question 4- What actions need to be scheduled between now and 2021 to acquire missing evidence and make the integration of primary and secondary prevention practically possible?

4. Recommendations for the reorganisation of cervical cancer screening

Screening must be re-organised from 2021 and the first changes must already be arranged.

For girls vaccinated in their twelfth year (±1 year), i.e. at an age in which the probability of already having had sexual intercourse is very low, a combined sequential strategy is proposed:

A. A tailored strategy, which involves the availability of a link between vaccination registers and screening programs. In this way, both girls vaccinated in their twelfth year and screening programs can count on a better cost-efficacy ratio;
B. A uniform strategy, which can be adopted when the Regional or local coverage data have reached the threshold, which should be defined on the basis of the population effectiveness (including the herd effect) of the HPV vaccine in Italy and in the other countries where monitoring is in progress. With this approach, the Regions that reach the objective will have a greater advantage with respect to the tailored screening strategy in terms of lower system complexity.

Vaccination coverage is an indicator that may change over time and not be uniform within the same Region. This variability must also be considered. The minimum coverage threshold may be subject to future assessment according to an improved understanding of the resulting protection, also for non-vaccinated subjects, due to herd immunity. This would also improve substantially through the possible extension of vaccination to Italian adolescent males. Screening and vaccination services must be coordinated and the respective staff must be adequately trained on the rationale of the new protocols.

With a screening starting age delayed to 30 years, women vaccinated in their 12th year would start screening at an age in which in Italy and in Europe the HPV test is already recommended as a primary test.

It is likely that the interval between screening tests will be extended, but this possibility must be assessed with a research project, in order to guarantee optimal protection with the lowest possible number of tests.

Compared to the 14 screening episodes envisaged with traditional cytological screening, women with HPV screening will undergo, over 40 years of life, to up 9 screening episodes if they are not vaccinated and even less if they are vaccinated. Therefore, extending the current interval between screening from three to five years, delaying the start of the program to the age of 30 for women vaccinated in their 12th year, and the possible further extension of intervals for vaccinated women - based on the evidence acquired in the meantime - will lead to a change and to a progressive reduction in the workloads of screening programs (coordinating centres, first-level clinics, laboratories, pathology and gynecology units). This will increase the sustainability of the programs over time and lead to a more efficient use of resources.

The proposals to change protocols as per the previous questions are applicable to the cohorts of girls vaccinated in their 12th year. In the cohorts vaccinated in their fifteenth year or later, screening will still start at age 25 with the Pap test.

5. Recommendations for implementation and research

The jury fully accepted the proposals for the implementation and research of the Scientific Technical Committee (see Table 3). In fact, it supported with full consent the need to launch programmatic monitoring

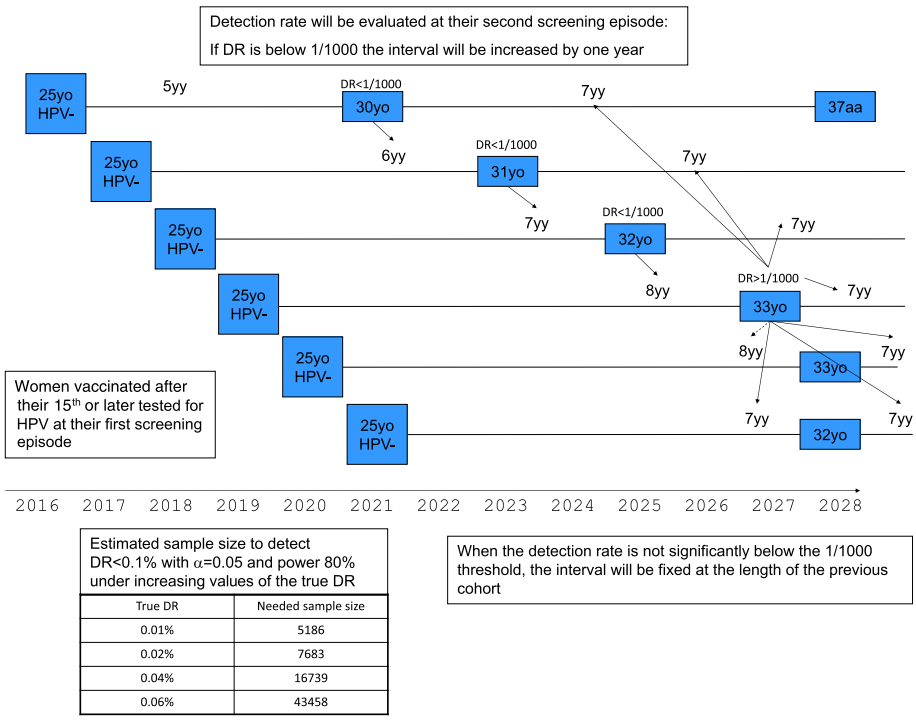

Fig. 3. Study design and sample size estimation for gradually extending the screening interval in vaccinated and HPV-negative women.

and study actions at regional level and, in particular, to integrate vaccination registers, screening registers and cancer registers, for which central planning and support interventions are required.

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Conflict of interest

PGR as principal investigator of an independent study funded by the Italian Ministry of Health, conducted negotiations with Abbott, Hologic-Genprobe, Roche Diagnostics, Qiagen to obtain reagents at reduced price of for free.

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References

Agarossi, A., Ferrazzi, E., Parazzini, F., Perno, C.F., Ghisoni, L., 2009. Prevalence and type distribution of high-risk human papillomavirus infection in women undergoing voluntary cervical cancer screening in Italy. J. Med. Virol. 81:529–535 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/19152401.

AIRTUM, 2015. ITACAN. ([cited 2015 Jul 9]; (Available from). http://itacan.ispo.toscana.it/italian/itacan.htm.

Australian Institute of Health and Welfare, 2013. Cervical screening in Australia 2010–2011. National Cervical Screening Program. ([cited 2014 Jun 4]; Available from) http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129543399).

Baldur-Felskov, B., Dehlendorff, C., Junge, J., Munk, C., Kjaer, S., 2014. Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program. Cancer Causes Control 25:915–922 (Available from) https://www.ncbi.nlm.nih.gov/pubmed/24797870.

Brotherton, J.M.L., Saville, A.M., May, C.L., Chappell, G., Gertig, D.M., 2015. Human papillomavirus vaccination is changing the epidemiology of high-grade cervical lesions in Australia. Cancer Causes Control 26:953–954 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25804857.

Brown, P., Brunnhuber, K., Chalkidou, K., Chalmers, I., Clarke, M., Fenton, M., Forbes, C., Glanville, J., Hicks, N.J., Moody, J., Twaddle, S., Timimi, H., et al., 2006. How to formulate research recommendations. BMJ 333:804–806. http://dx.doi.org/10.1136/bmj.38987.492014.94 (Available from) http://www.ncbi.nlm.nih.gov/pubmed/17038740.

Bruni, L., Barrionuevo-Rosas, L., Albero, G., Aldea, M., Serrano, B., Valencia, S., Brotons, M., Mena, M., Cosano, R., Muñoz, J., Bosch, F.X., de Sanjose, S., et al., 2015. Human papillomavirus and related diseases in Europe. Summary Report 2015-04-08 ([cited 2015 Jul 9];Available from). http://www.hpvcentre.net/statistics/reports/XEX.pdf.

Capra, G., Giovannelli, L., Bellavia, C., Migliore, M.C., Caleca, M.P., Perino, A., Ammatuna, P., 2008. HPV genotype prevalence in cytologically abnormal cervical samples from women living in south Italy. Virus Res. 133:195–200 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/18282628.

Carozzi, F.M., Tornesello, M.L., Burroni, E., Loquercio, G., Carillo, G., Angeloni, C., Scalisi, A., Macis, R., Chini, F., Buonaguro, F.M., Giorgi Rossi, P., 2010. HPV Prevalence Italian Working Group. Prevalence of human papillomavirus types in high-grade cervical intraepithelial neoplasia and cancer in Italy. Cancer Epidemiol Biomarkers Prev. A Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 19:2389–2400. http://www.ncbi.nlm.nih.gov/pubmed/20826836. 10.1158/1055-9965.EPI-10-0131 (Available from).

Castle, P.E., Rodríguez, A.C., Burk, R.D., Herrero, R., Wacholder, S., Alfaro, M., Morales, J., Guillen, D., Sherman, M.E., Solomon, D., Schiffman, M., 2009. Proyecto Epidemiológico Guanacaste (PEG) Group. Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. BMJ 339, b2569 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/19638649. 10.1136/bmj.b2569.

Castle, P.E., Stoler, M.H., Wright, T.C., Sharma, A., Wright, T.L., Behrens, C.M., 2011. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol. 12:880–890 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/21865084.

Chow, E.P.F., Read, T.R.H., Wigan, R., Donovan, B., Chen, M.Y., Bradshaw, C.S., Fairley, C.K., 2015. Ongoing decline in genital warts among young heterosexuals 7 years after the Australian human papillomavirus (HPV) vaccination programme. Sex. Transm. Infect. 91:214–219 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25305210.

Ciotti, M., Paba, P., Bonifacio, D., Di Bonito, L., Benedetto, A., Favalli, C., 2006. Single or multiple HPV types in cervical cancer and associated metastases. Oncol. Rep. 15:143–148 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/16328047.

Clifford, G.M., Smith, J.S., Aguado, T., Franceschi, S., 2003a. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br. J. Cancer 89:101–105 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/12838308.

Clifford, G.M., Smith, J.S., Plummer, M., Muñoz, N., Franceschi, S., 2003b. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br. J. Cancer 88:63–73 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/12556961.

CNESPS, ISS, 2015a. Survey PASSI 2011–14. ([cited 2015 Jul 9]; Available from). http://www.epicentro.iss.it/passi/dati/ScreeningCervicale.asp.

CNESPS, ISS, 2015b. Stato di avanzamento della campagna vaccinale per l'HPV: dati di copertura vaccinale al 31/12/2014 – Rapporto semestrale (dati aggiornati di tutte le Regioni). ([cited 2015 Jul 9]; Available from). http://www.epicentro.iss.it/temi/vaccinazioni/dati_Ita.asp?tab-container-1=tab113.

Commissione Oncologica Nazionale. Proposte operative in tema di prevenzione secondaria del cervico-carcinoma uterino. In: "Linee guida elaborate dalla Commissione Oncologica Nazionale, in applicazione di quanto previsto dal Piano Sanitario Nazionale per il triennio 1994–96, relativo all'a. 1996." (Gazzetta Ufficiale n.127 del 1-6-1996 - Suppl. Ordinario n. 88. Available from http://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario;jsessionid=rO6j509WttetHl7DfPpZkA__.ntc-as5-guri2b?atto.dataPubblicazioneGazzetta=1996-06-01&atto.codiceRedazionale=096A3281&elenco30giorni=false;).

CSS, 2015. Piano Nazionale Prevenzione Vaccinale 2016–2018. (Available from). http://www.quotidianosanita.it/allegati/allegato1955037.pdf.

De Carvalho, N., Teixeira, J., Roteli-Martins, C.M., Naud, P., De Borba, P., Zahaf, T., Sanchez, N., Schuind, A., 2010. Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. Vaccine 28:6247–6255 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/20643092.

de Sanjose, S., Quint, W.G., Alemany, L., Geraets, D.T., Klaustermeier, J.E., Lloveras, B., Tous, S., Felix, A., Bravo, L.E., Shin, H.-R., Vallejos, C.S., de Ruiz, P.A., et al., 2010. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 11:1048–1056. http://www.ncbi.nlm.nih.gov/pubmed/20952254. 10.1016/S1470-2045(10)70230-8 (Available from).

de Sanjose, S., Alemany, L., Tous, S., Bosch, F.X., HPV RIS TT Study Group, 2011. HPV types in early-onset cervical cancer – Authors' reply. Lancet Oncol. 12, 117–118.

Del Mistro, A., Salamanca, H.F., Trevisan, R., Bertorelle, R., Parenti, A., Bonoldi, E., Zambon, P., Minucci, D., 2006. Human papillomavirus typing of invasive cervical cancers in Italy. Infect. Agent Cancer 1:9 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/17192187.

Deleré, Y., Wichmann, O., Klug, S.J., van der Sande, M., Terhardt, M., Zepp, F., Harder, T., 2014. The efficacy and duration of vaccine protection against human papillomavirus: a systematic review and meta-analysis. Dtsch. Arztebl. Int. 111:584–591 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25249360.

Dobson, S.R.M., McNeil, S., Dionne, M., Dawar, M., Ogilvie, G., Krajden, M., Sauvageau, C., Scheifele, D.W., Kollmann, T.R., Halperin, S.A., Langley, J.M., Bettinger, J.A., et al., 2013. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 309:1793–1802 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/23632723.

Donati, S., Giambi, C., Declich, S., Salmaso, S., Filia, A., Ciofi degli Atti, M.L., Alibrandi, M.P., Brezzi, S., Carozzi, F., Collina, N., Franchi, D., Lattanzi, A., et al., 2012. Knowledge, attitude and practice in primary and secondary cervical cancer prevention among young adult Italian women. Vaccine 30:2075–2082 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22300719.

Drolet, M., Bénard, É., Boily, M.-C., Ali, H., Baandrup, L., Bauer, H., Beddows, S., Brisson, J., Brotherton, J.M.L., Cummings, T., Donovan, B., Fairley, C.K., et al., 2015. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect. Dis. 15:565–580 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25744474. 10.1016/S1473-3099(14)71073-4.

Ferris, D., Samakoses, R., Block, S.L., Lazcano-Ponce, E., Restrepo, J.A., Reisinger, K.S., Mehlsen, J., Chatterjee, A., Iversen, O.-E., Sings, H.L., Shou, Q., Sausser, T.A., et al., 2014. Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics 134:e657–e665 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25136050.

Franco, E.L., Mahmud, S.M., Tota, J., Ferenczy, A., Coutlée, F., 2009. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. Arch. Med. Res. 40:478–485 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/19853188.

Gargiulo, F., De Francesco, M.A., Schreiber, C., Ciravolo, G., Salinaro, F., Valloncini, B., Manca, N., 2007. Prevalence and distribution of single and multiple HPV infections in cytologically abnormal cervical samples from Italian women. Virus Res. 125: 176–182 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/17257705.

Garzetti, G.G., Ciavattini, A., Lucarini, G., Goteri, G., Menso, S., De Nictolis, M., Romanini, C., Biagini, G., 1998. The role of human papillomavirus DNAs in cervical carcinoma and risk of lymph node metastasis: association with 72-kilodalton metalloproteinase immunostaining. Cancer 82:886–892 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/9486578.

Giambi, C., 2014. Stato di avanzamento della campagna vaccinale per l'HPV: dati di copertura vaccinale al 31/12/2014 - Rapporto semestrale (dati aggiornati di tutte le Regioni). ([cited 2015 Jul 9]; Available from). http://www.epicentro.iss.it/problemi/hpv/pdf/Aggiornamento_HPV_31122014Completo.pdf.

Giambi, C., Del Manso, M., De Mei, B., D'Ancona, F., Giovanelli, I., Cattaneo, C., Possenti, V., Declich, S., 2013. Gruppo di lavoro VALORE. Progetto VALORE (VAlutazione LOcale e REgionale delle campagne di vaccinazione contro l'HPV): favorire l'adesione consapevole alla vaccinazione. ([cited 2015 Jul 9]; Available from). http://www.iss.it/binary/publ/cont/13_47_web.pdf.

Giorgi Rossi, P., Bisanzi, S., Paganini, I., Di Iasi, A., Angeloni, C., Scalisi, A., Macis, R., Pini, M.T., Chini, F., Carozzi, F.M., 2010. HPV Prevalence Italian Working Group. Prevalence of HPV high and low risk types in cervical samples from the Italian general population: a population based study. BMC Infect. Dis. 10:214 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/20646310.

Giorgi Rossi, P., Sideri, M., Carozzi, F.M., Vocaturo, A., Buonaguro, F.M., Tornesello, M.L., Burroni, E., Mariani, L., Boveri, S., Zaffina, L.M., Chini, F., 2012a. HPV Prevalence Italian Working Group. HPV type distribution in invasive cervical cancers in Italy: pooled analysis of three large studies. Infect. Agent Cancer 7:26. http://www.ncbi.nlm.nih.gov/pubmed/23110797. 10.1186/1750-9378-7-26 (Available from).

Giorgi Rossi, P., Chini, F., Borgia, P., Guasticchi, G., Carozzi, F.M., Confortini, M., Angeloni, C., Buzzoni, C., Buonaguro, F.M., Gruppo di lavoro HPV Prevalenza, 2012b. Human Papilloma Virus (HPV), cervical cancer incidence and screening uptake: differences among Northern, Central and Southern Italy. Epidemiol. Prev. 36:108–119 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22706361.

Giorgi Rossi, P., Caroli, S., Mancini, S., de' Bianchi, P.S., Finarelli, A.C., Naldoni, C., Bucchi, L., 2015. FFE-R cervical cancer screening and pathology registry group. Screening history of cervical cancers in Emilia-Romagna, Italy: defining priorities to improve cervical cancer screening. Eur. J. Cancer Prev. 24:128–134. https://www.ncbi.nlm.nih.gov/pubmed/24787379. 10.1097/CEJ.0000000000000035 (Available at).

GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski, B., de Borba, P.C., Naud, P.S., Roteli-Martins, C.M., De Carvalho, N.S., Teixeira, J.C., Aoki, F., Ramjattan, B., Shier, R.M., Somani, R., Barbier, S., et al., 2009. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet 374:1975–1985 ((London, England) Available from). http://www.ncbi.nlm.nih.gov/pubmed/19962185.

Guan, P., Howell-Jones, R., Li, N., Bruni, L., de Sanjosé, S., Franceschi, S., Clifford, G.M., 2012. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int. J. Cancer 131:2349–2359 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22323075.

Guan, P., Clifford, G.M., Franceschi, S., 2013. Human papillomavirus types in glandular lesions of the cervix: a meta-analysis of published studies. Int. J. Cancer 132:248–250 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22684765.

Harper, D.M., 2008. Impact of vaccination with Cervarix (trade mark) on subsequent HPV-16/18 infection and cervical disease in women 15–25 years of age. Gynecol. Oncol. 110:S11–S17 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/18649932.

Intesa tra il Governo, le Regioni e le Province autonome di Trento e Bolzano, 2015. Piano Nazionale Prevenzione Vaccinale (PNPV) 2012–2014. Intesa ai sensi dell'articolo 8, comma 6, della legge 5 giugno 2003, n°131. http://www.statoregioni.it/Documenti/DOC_035260_54csrpunto4.pdf ([cited 2015 Jul 9]; Available from).

Intesa tra il Governo le Regioni e le Provincie autonome, 2007. Strategie per l'offerta attiva del vaccino contro l'infezione da HPV in Italia. ([cited 2015 Jul 9]; Available from). http://www.statoregioni.it/Documenti/DOC_016696_264cse.pdf.

Joura, E.A., Giuliano, A.R., Iversen, O.-E., Bouchard, C., Mao, C., Mehlsen, J., Moreira, E.D., Ngan, Y., Petersen, L.K., Lazcano-Ponce, E., Pitisuttithum, P., Restrepo, J.A., et al., 2015. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N. Engl. J. Med. 372:711–723 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25693011.

Kavanagh, K., Pollock, K.G.J., Potts, A., Love, J., Cuschieri, K., Cubie, H., Robertson, C., Donaghy, M., 2014. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br. J. Cancer 110:2804–2811 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/24736582.

Khan, M.J., Castle, P.E., Lorincz, A.T., Wacholder, S., Sherman, M., Scott, D.R., Rush, B.B., Glass, A.G., Schiffman, M., 2005. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J. Natl. Cancer Inst. 97: 1072–1079. http://www.ncbi.nlm.nih.gov/pubmed/16030305. 10.1093/jnci/dji187 (Available from).

Kjær, S.K., Frederiksen, K., Munk, C., Iftner, T., 2010. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J. Natl. Cancer Inst. 102:1478–1488. http://www.ncbi.nlm.nih.gov/pubmed/20841605. 10.1093/jnci/djq356 (Available from).

Kreimer, A.R., Struyf, F., Del Rosario-Raymundo, M.R., Hildesheim, A., Skinner, S.R., Wacholder, S., Garland, S.M., Herrero, R., David, M.-P., Wheeler, C.M., 2015. Costa Rica Vaccine Trial and PATRICIA study groups. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. Lancet Oncol. 16:775–786 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/26071347.

Laconi, S., Greco, M., Milia, G., Pellegrini-Bettoli, P., Pani, P., Laconi, E., Rais, M., 2000. Simultaneous detection and typing of human papillomavirus in cervical biopsies using PCR-reverse hybridization. Pathologica 92:524–529 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/11234303.

Lehtinen, M., Dillner, J., 2013. Clinical trials of human papillomavirus vaccines and beyond. Nat. Rev. Clin. Oncol. 10:400–410. http://www.ncbi.nlm.nih.gov/pubmed/23736648 (Available from).

Li, N., Franceschi, S., Howell-Jones, R., Snijders, P.J.F., Clifford, G.M., 2011. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. Int. J. Cancer 128: 927–935 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/20473886.

Lillo, F., Galli, L., Lodini, S., Taccagni, G., Ferrari, A., Origoni, M., 2008. Extralesional detection and load of human papillomavirus DNA: a possible marker of preclinical tumor spread in cervical cancer. J. Low. Genit. Tract. Dis. 12:204–209 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/18596462.

Lipsitch, M., 1999. Bacterial vaccines and serotype replacement: lessons from Haemophilus influenzae and prospects for Streptococcus pneumoniae. Emerg. Infect. Dis. 5: 336–345 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/10341170.

Lu, B., Kumar, A., Castellsagué, X., Giuliano, A.R., 2011. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infect. Dis. 11:13 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/21226933.

Luna, J., Plata, M., Gonzalez, M., Correa, A., Maldonado, I., Nossa, C., Radley, D., Vuocolo, S., Haupt, R.M., Saah, A., 2013. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil™ in adult women. PLoS One 8, e83431 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/24391768.

Mariani, L., Monfulleda, N., Alemany, L., Vizza, E., Marandino, F., Vocaturo, A., Benevolo, M., Quirós, B., Lloveras, B., Klaustermeier, J.E., Quint, W., de Sanjosé, S., et al., 2010. Human papillomavirus prevalence and type-specific relative contribution in invasive cervical cancer specimens from Italy. BMC Cancer 10:259 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/20525370.

Naud, P.S., Roteli-Martins, C.M., De Carvalho, N.S., Teixeira, J.C., de Borba, P.C., Sanchez, N., Zahaf, T., Catteau, G., Geeraerts, B., Descamps, D., 2014. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Hum. Vaccin. Immunother. 10:2147–2162 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25424918.

Olsson, S.-E., Villa, L.L., Costa, R.L.R., Petta, C.A., Andrade, R.P., Malm, C., Iversen, O.-E., Høye, J., Steinwall, M., Riis-Johannessen, G., Andersson-Ellstrom, A., Elfgren, K., et al., 2007. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine 25:4931–4939. http://www.ncbi.nlm.nih.gov/pubmed/17499406. 10.1016/j.vaccine.2007.03.049 (Available from).

ONS, 2015. Programmi di screening in Italia 2014. ([cited 2015 Jul 9]; Available from). http://www.osservatorionazionalescreening.it/sites/default/files/allegati/screening_matite_2.pdf#overlay-context=content/i-rapporti-brevi-dell%25E2%2580%2599ons.

Paavonen, J., Jenkins, D., Bosch, F.X., Naud, P., Salmerón, J., Wheeler, C.M., Chow, S.-N., Apter, D.L., Kitchener, H.C., Castellsague, X., de Carvalho, N.S., Skinner, S.R., et al., 2007. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 369: 2161–2170 ((London, England) Available from). http://www.ncbi.nlm.nih.gov/pubmed/17602732.

Palmroth, J., Merikukka, M., Paavonen, J., Apter, D., Eriksson, T., Natunen, K., Dubin, G., Lehtinen, M., 2012. Occurrence of vaccine and non-vaccine human papillomavirus types in adolescent Finnish females 4 years post-vaccination. Int. J. Cancer 131: 2832–2838 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22492244.

Pollock, K.G.J., Kavanagh, K., Potts, A., Love, J., Cuschieri, K., Cubie, H., Robertson, C., Cruickshank, M., Palmer, T.J., Nicoll, S., Donaghy, M., et al., 2014. Br. J. Cancer 111: 1824–1830 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25180766.

Rolla, M., Berretta, R., Patrelli, T.S., Merisio, C., Gramellini, D., Fadda, G.M., Bacchi Modena, A., Nardelli, G.B., 2009. A perspective study on correlation between HPV DNA and lymph nodes in surgically treated cervical carcinoma patients. Preliminary data. Eur. J. Gynaecol. Oncol. 30:557–561 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/19899415.

Romanowski, B., 2011. Long term protection against cervical infection with the human papillomavirus: review of currently available vaccines. Hum. Vaccin. 7:161–169 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/21307652.

Ronco, G., Biggeri, A., Confortini, M., Naldoni, C., Segnan, N., Sideri, M., Zappa, M., Zorzi, M., Calvia, M., Accetta, G., Giordano, L., Cogo, C., et al., 2012. Health technology assessment report: HPV DNA based primary screening for cervical cancer precursors. Epidemiol. Prev. 36:e1–72 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22828243.

Ronco, G., Dillner, J., Elfström, K.M., Tunesi, S., Snijders, P.J.F., Arbyn, M., Kitchener, H., Segnan, N., Gilham, C., Giorgi-Rossi, P., Berkhof, J., Peto, J., et al., 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 383:524–532 (London, England). http://www.ncbi.nlm.nih.gov/pubmed/24192252. 10.1016/S0140-6736(13)62218-7 (Available from).

Roteli-Martins, C.M., Naud, P., De Borba, P., Teixeira, J.C., De Carvalho, N.S., Zahaf, T., Sanchez, N., Geeraerts, B., Descamps, D., 2012. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. Hum. Vaccin. Immunother. 8:390–397 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/22327492.

Sandø, N., Kofoed, K., Zachariae, C., Fouchard, J., 2014. A reduced national incidence of anogenital warts in young Danish men and women after introduction of a national quadrivalent human papillomavirus vaccination programme for young women—an ecological study. Acta Derm. Venereol. 94:288–292 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/24150529.

Sandri, M.T., Riggio, D., Salvatici, M., Passerini, R., Zorzino, L., Boveri, S., Radice, D., Spolti, N., Sideri, M., 2009. Typing of human papillomavirus in women with cervical lesions: prevalence and distribution of different genotypes. J. Med. Virol. 81:271–277 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/19107962.

Schiffman, M., Glass, A.G., Wentzensen, N., Rush, B.B., Castle, P.E., Scott, D.R., Buckland, J., Sherman, M.E., Rydzak, G., Kirk, P., Lorincz, A.T., Wacholder, S., et al., 2011. A long-term prospective study of type-specific human papillomavirus infection and risk of cervical neoplasia among 20,000 women in the Portland Kaiser Cohort Study. Cancer Epidemiol Biomarkers Prev. A Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 20:1398–1409. http://www.ncbi.nlm.nih.gov/pubmed/21602310. 10.1158/1055-9965 (Available from).

Schwarz, T., Spaczynski, M., Kaufmann, A., Wysocki, J., Gałaj, A., Schulze, K., Suryakiran, P., Thomas, F., Descamps, D., 2015. Persistence of immune responses to the HPV-16/18 AS04-adjuvanted vaccine in women aged 15–55 years and first-time modelling of antibody responses in mature women: results from an open-label 6-year follow-up study. BJOG Int J Obstet Gynaecol 122:107–118 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/25208608.

Serraino, D., Gini, A., Taborelli, M., Ronco, G., Giorgi-Rossi, P., Zappa, M., Crocetti, E., Franzo, A., Falcini, F., Visioli, C.B., Stracci, F., Zorzi, M., et al., 2015. Changes in cervical cancer incidence following the introduction of organized screening in Italy. Prev. Med. 75: 56–63. http://www.ncbi.nlm.nih.gov/pubmed/25818232. 10.1016/j.ypmed.2015.01.034 ((Baltim) Available from).

Sideri, M., Cristoforoni, P., Casadio, C., Boveri, S., Igidbashian, S., Schmitt, M., Gheit, T., Tommasino, M., 2009. Distribution of human papillomavirus genotypes in invasive cervical cancer in Italy: a representative, single institution case series. Vaccine 27 (Suppl. 1):A30–A33 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/19480958.

Smith, J.S., Lindsay, L., Hoots, B., Keys, J., Franceschi, S., Winer, R., Clifford, G.M., 2007. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int. J. Cancer 121:621–632 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/17405118.

Spinillo, A., Gardella, B., Roccio, M., Alberizzi, P., Silini, E.M., Dal, B.B., 2014. Untypable human papillomavirus infection and risk of cervical intraepithelial neoplasia among women with abnormal cervical cytology. J. Med. Virol. 86:1145–1152 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/24692002.

Tabrizi, S.N., Brotherton, J.M.L., Kaldor, J.M., Skinner, S.R., Cummins, E., Liu, B., Bateson, D., McNamee, K., Garefalakis, M., Garland, S.M., 2012. Fall in human papillomavirus prevalence following a national vaccination program. J. Infect. Dis. 206:1645–1651 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/23087430.

The FUTURE II Study Group, 2007. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N. Engl. J. Med. 356:1915–1927 ([cited 2015 Oct 10]Available from). 10.1056/NEJMoa061741.

Thomsen, L.T., Frederiksen, K., Munk, C., Junge, J., Iftner, T., Kjaer, S.K., 2015. Long-term risk of cervical intraepithelial neoplasia grade 3 or worse according to high-risk human papillomavirus genotype and semi-quantitative viral load among 33,288 women with normal cervical cytology. Int. J. Cancer 137:193–203. http://www.ncbi.nlm.nih.gov/pubmed/25471319. 10.1002/ijc.29374 (Available from).

Tornesello, M.L., Duraturo, M.L., Botti, G., Greggi, S., Piccoli, R., De Palo, G., Montella, M., Buonaguro, L., Buonaguro, F.M., Italian, H.P.V., 2006. Working Group. Prevalence of alpha-papillomavirus genotypes in cervical squamous intraepithelial lesions and invasive cervical carcinoma in the Italian population. J. Med. Virol. 78:1663–1672 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/17063505.

Tornesello, M.L., Losito, S., Benincasa, G., Fulciniti, F., Botti, G., Greggi, S., Buonaguro, L., Buonaguro, F.M., 2011. Human papillomavirus (HPV) genotypes and HPV16 variants and risk of adenocarcinoma and squamous cell carcinoma of the cervix. Gynecol. Oncol. 121:32–42 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/21211829.

Tota, J., Mahmud, S.M., Ferenczy, A., Coutlée, F., Franco, E.L., 2010. Promising strategies for cervical cancer screening in the post-human papillomavirus vaccination era. Sex. Health 7:376–382 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/20719230.

Venturoli, S., Ambretti, S., Cricca, M., Leo, E., Costa, S., Musiani, M., Zerbini, M., 2008. Correlation of high-risk human papillomavirus genotypes persistence and risk of residual or recurrent cervical disease after surgical treatment. J. Med. Virol. 80:1434–1440 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/18551620.

Villa, L.L., Costa, R.L.R., Petta, C.A., Andrade, R.P., Paavonen, J., Iversen, O.-E., Olsson, S.-E., Høye, J., Steinwall, M., Riis-Johannessen, G., Andersson-Ellstrom, A., Elfgren, K., et al., 2006. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br. J. Cancer 95:1459–1466. http://www.ncbi.nlm.nih.gov/pubmed/17117182. 10.1038/sj.bjc.6603469 (Available from).

Voglino, G., Poso, F., Privitera, S., Parisio, F., Ghiringhello, B., Gordini, G., Chiara, G., Massobrio, M., Fessia, L., 2000. The role of human papillomavirus in cyto-histological practice: distribution and prevalenceof hig-risk strains (16, 18, 31, 33, and 35) in intraepithelial lesions and neoplasia of the uterine cervix. Pathologica 92:516–523 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/11234302.

von Karsa, L., Arbyn, M., De Vuyst, H., Dillner, J., Dillner, L., Franceschi, S., Patnick, J., Ronco, G., Segnan, N., Suonio, E., Törnberg, S., Anttila, A., 2015. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus Res. 1:22–31 [cited 2015 Dec 29] Available from). http://www.sciencedirect.com/science/article/pii/S2405852115000129.

WHO/RHR, 2006. Preparing for the Introduction of HPV Vaccines: Policy and Programme Guidance for Countries. ([cited 2015 Jul 9];Available from). http://www.who.int/reproductivehealth/publications/cancers/RHR_06.11/en/.

Zerbini, M., Venturoli, S., Cricca, M., Gallinella, G., De Simone, P., Costa, S., Santini, D., Musiani, M., 2001. Distribution and viral load of type specific HPVs in different cervical lesions as detected by PCR-ELISA. J. Clin. Pathol. 54:377–380 (Available from). http://www.ncbi.nlm.nih.gov/pubmed/11328837.