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The possible effects on socio-economic inequalities of introducing HPV-testing as primary test in cervical cancer screening programs.

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Abstract

Background
Screening with HPV is more effective than Pap test in preventing cervical cancer. HPV as primary test will imply longer intervals and a triage test for HPV positive women. It will also permit the development of self-sampling devices. These innovations may affect population coverage, participation, and compliance to protocols, and likely in a different way for less educated, poorer, and disadvantaged women.

Aim
To describe the impact on inequalities, actual or presumed, of the introduction of HPV-based screening.

Methods
The putative HPV-based screening algorithm has been analysed to identify critical points for inequalities. A systematic review of the literature has been conducted searching PubMed on HPV screening coverage, participation, and compliance. Results were summarised in a narrative synthesis.

Results
Knowledge about HPV and cervical cancer was lower in women with low Socio-economic status and in disadvantaged groups. A correct communication can reduce differences.
Longer intervals will make it easier to achieve high-population coverage, but higher cost of the test in private providers could reduce the use of opportunistic screening by disadvantaged women.
There are some evidences that inviting for HPV test instead of Pap increases participation, but there are no data on social differences.
Self-sampling devices are effective in increasing participation and coverage. Some studies showed that the acceptability of self-sampling is higher in more educated women, but there is also an effect on hard-to-reach women.
Communication of HPV positivity may increase anxiety and impact on sexual behaviours, the effect is stronger in low educated and disadvantaged women.
Finally, many studies found indirect evidence that unvaccinated women are or will be more probably under-screened.

Conclusions
The introduction of HPV test may increase population coverage, but non-compliance to protocols and interaction with opportunistic screening can increase the existing inequalities.
Background

Cervical cancer is still the third cancer worldwide in terms of incidence, although the burden of disease is not evenly distributed, with about 80% of cases occurring in low-income countries (IARC 2008). In industrialised countries, instead, incidence and mortality have been dramatically reduced thanks to Pap test and screening programs (Arbyn M et al. 2008; IARC 2005). In fact, the Pap test is able to identify cytological abnormalities exfoliated from pre-cancerous lesions, and progression to cervical cancer is prevented through outpatient treatment (Arbyn M et al. 2008; IARC 2005). Persistent infection with HPV oncogenic types has been demonstrated to be the necessary, but not sufficient, cause of cervical cancer (IARC 2005). Knowledge of the natural history of the disease has led to the introduction of two new tools for cervical cancer prevention: vaccine and HPV test for screening (zur Hausen H 2002).

Population-based randomised trials have shown that screening with HPV as primary test is more effective than Pap test in reducing cervical cancer incidence (Ronco G et al. 2013) and mortality (Sankaranarayanan R et al. 2009).

The accuracy characteristics of the HPV DNA test are different from those of the Pap test. First and foremost, the former is more sensitive and less specific (Cuzick J et al. 2008). Further, it has a higher prospective negative predictive value, i.e. the risk of having a CIN3 or cancer five years after an HPV negative test is still lower than the risk three years after a negative Pap test (Dillner J et al. 2008; Ronco G et al. 2013). Due to lower specificity a higher number of women will need further ascertainment. However, few of them will have a high-grade lesion and direct referral to colposcopy may thus be too intensive an approach (Ronco G et al. 2012; Health Council of The Netherlands 2011; Cuzick J et al. 2012). On the other hand, higher sensitivity and prospective negative predictive value will allow longer intervals (Dillner J et al. 2008; Ronco G et al. 2013). HPV infection can persist for several years before its clearance or progression to a high-grade lesion requiring treatment; women with long-term persistent infections need to be followed up with reasonable protocols, adapted to their risk of developing cancer (Castle P et al. 2008).

Therefore the shift from Pap test to HPV test as primary screening test will dramatically change the screening program protocols and organization: the intervals will be longer, and a triage test for HPV positive women and more complex algorithms for the management of positive women will be needed. Furthermore, the introduction of HPV test will result in less intensive protocols and follow up. Finally, a molecular test makes it possible to develop self-sampling devices.
All these changes and technical innovations may affect screening participation and population coverage (Cuzick J et al. 2012; Philips Z et al. 2006), and most likely in a different way for less educated, poorer, and more disadvantaged women (Lazcano-Ponce E et al. 2009; Scarinci IC et al. 2010; Bekkers RL et al. 2006). 

To date only few countries have introduced the HPV test in the organised screening protocol and none has yet implemented such protocols at a national level; several countries have large-scale population-based pilot projects under way (Zorzi et al. 2013; NHSCSP 2012; Rijkaart et al. 2012; Leinonen et al. 2012; Confortini et al. 2010).

**Objective**

To identify the possible effect of the introduction of HPV-based protocols in organised screening program on social inequalities by means of an analysis of the process and of a systematic review of the literature. The analysis is focused on countries with public organised screening programs.

**Methods**

*Definition of the putative algorithm for HPV-based screening.*

After an initial search of the meta-literature (systematic reviews, HTA reports, guidelines and narrative reviews) on implementing an HPV-based screening and social inequalities in cervical cancer prevention, we analysed the putative screening algorithm with HPV as primary screening, as included in the upcoming European Guidelines (Ronco G et al. 2012), to identify all the critical points where inequalities in coverage, participation and compliance to protocols, and in the effectiveness of screening program could be generated or reduced.

*Scope*

To define the scope of the systematic review we analysed the flowchart of the algorithm to identify those points where new inequalities might be introduced and/or where existing inequalities might be reduced. Relevant topics should have two characteristics: 1) there should be a noticeable change with the introduction of the HPV-based screening; 2) the topic should be potentially related to socioeconomic inequalities. Among the parameters measuring the effectiveness of an organised screening program, test coverage, participation, and compliance have a "per se" effect on equity (Ronco G et al. 2012).
A systematic review of the literature was conducted on PubMed and the European public screening program websites to identify relevant publications on HPV screening and coverage, participation, and compliance.

The PubMed search strategy was defined according to the methods used in two previous systematic reviews, one on the methods to increase participation in screening (Ronco G et al. 2012; Camilloni L et al. 2013; Ferroni E et al. 2012) the other on inequalities and screening (Spada T et al. 2010). To the original search of the systematic review on methods to increase participation we added terms to identify those focusing on inequalities as well as terms to specify HPV-based screening (HPV or human papillomavirus). The references of all the relevant papers were checked to identify other potentially relevant papers.

The search was limited to the period from 1/1/2000 to 31/7/2013. The rationale for limiting the search to 2000 is that in the 1990s there were no population-based experiences of HPV screening. Furthermore, the screening algorithms now proposed in organised screening were defined in the early 2000s (Cuzick J et al 2003).

From the studies retrieved we first selected those that were potentially relevant by reading the abstract. The abstract should present data or hypothesis on association or interaction between HPV knowledge, HPV screening attendance and/or attitude AND social, cultural, economic, and/or ethnic inequalities. Due to resource limitations, the title and abstract screening were carried out by only one researcher (FB) and subsequently checked by a second author (PGR) by crosschecking the references. The full text of the relevant studies were then analysed to identify and classify the information or hypothesis reported. A further number of studies was excluded in this step because the discussion of HPV and inequalities was too vague or because the paper focused exclusively on vaccination campaigns. The inclusion criteria were evaluated by two authors independently (FB and PGR); discordant cases were discussed to reach an agreement.

We did not perform any quality analysis since we were interested in identifying any issues that may be relevant, which could emerge even in low-quality papers.

Data extraction and narrative synthesis
From each paper the following data were extracted: publication year, author, title, topic(s) analysed, outcome considered, study design, population, synthesis of results, synthesis of the authors conclusions. Information from the selected papers was extracted according to its relevance with the topics listed in the flowchart analysis. Topics that emerged from the literature search and not postulated in the flowchart analysis were also identified and reported in the results. The papers were also classified according to the outcome considered: knowledge, test coverage, screening attitude and/or screening participation, compliance to protocols, and anxiety. In addition, we considered papers concerning the interactions between vaccine and screening. Systematic review results are summarised in a narrative synthesis.

Results

Flowchart analysis and search results

The critical points reported in figure 1 were identified in the preliminary analysis of the meta-literature. They can be grouped into four main topics: test coverage of the population, participation in screening program, compliance to the screening protocols and referral strategies, and communication of positive results and related anxiety. Of the papers treating the effects on test coverage and screening participation, a relevant number focused on the possible use of self-sampling. Furthermore, two topics not directly linked to the screening protocol were identified: knowledge and communication strategies of HPV and the interaction between screening and HPV vaccine.

One hundred and thirty-one abstracts were initially identified. Of these, 103 were considered relevant, with 81 included after full text examination (figure 2). During the literature analysis we summarised the information reported by each study according to the general issue for which it was relevant (figure 1).

Knowledge and communication strategies

The systematic review identified 23 studies on knowledge about HPV that reported differences in socioeconomic status levels or interaction between SES and effectiveness of information/communication tools or strategies. In general, the more deprived women, with lower educational level or SES, and women in more disadvantaged ethnic groups knew less about HPV and cervical cancer risk. Vanslyke and coll. (2008) found that knowledge of HPV was generally very limited among Hispanic women aged 18 to 60.
Furthermore, an indirect evidence of inequality among Hispanics came from the comparison of the Health Interview National Trends Survey (HINTS) and a cross-section of callers to the National Cancer Institute's (NCI) Cancer Information Service (CIS) (Kobetz E et al. 2010). Luque and coll. (2010) observed greater awareness of HPV and the HPV vaccine among Anglo American and Puerto Rican women than among Mexican and Honduran women. Al-Naggar and coll. (2010) examined the level of knowledge and barriers against cervical cancer screening of female university students in Selangor, Malaysia and found that age, marital status, ethnicity and monthly family income, were significantly associated with knowledge of cervical cancer screening. Vogtmann and coll. (2011) evaluated the demographic and behavioural factors associated with HPV awareness and knowledge in a population of Mexican college students and found that characteristics associated with not having heard about HPV were being male, not having running water, not having health insurance, and not having sexual experience. In the UK, Waller and coll. (2004) found that women and more educated people had better knowledge of the established risk factors for cervical cancer and HPV and in Germany, Klug and coll. (2005) found an association with social class. Only one study on Turkish sexual workers found almost no association between HPV knowledge and educational level (Ersan G et al. 2012).

Most of the studies were conducted before the introduction of HPV vaccine. Indeed, it is very likely that the knowledge and awareness of HPV strongly increased in the years around the introduction of mass vaccination campaigns in 2007-2009. This was confirmed by some focus groups conducted with women participating in the Florence, Italy cervical cancer screening in 2007 and 2011 (Cogo C et al. 2006; Iossa A 2010). It is also likely that the increase in knowledge was more relevant for less educated women who started out with a lower level of knowledge. Nevertheless, the PREGIO study, conducted in Italy during the launch of the mass vaccination of 12-year-old girls in 2008, found that knowledge of Pap test was still greater than the knowledge of HPV and cervical cancer, although more than 70% correctly answered questions on virus transmission and the role of HPV in cancerogenicity (Donati S et al. 2012). Women with higher educational level had greater knowledge about HPV and cervical cancer prevention but had similar attitudes towards undergoing vaccination. Two recent studies conducted in France (Haesebaert J et al. 2012) and Germany (Kuznetsov AV et al. 2012), instead, found there was still very little knowledge (16%) of the link between HPV and cervical cancer and an insufficient HPV awareness and low vaccination prevalence among young women.

Three trials and one case control study compared different strategies to provide information on HPV. Lloyd and coll. (2009) observed an increase in knowledge in 13-16-year-old girls with an increase in
fear but not in anxiety about infections after the distribution of a leaflet (not specific for HPV test and including other sexually transmitted diseases as well). Similar results were observed by Papa and coll. (2009) in women undergoing an HPV test and by Marek and coll. (2012) after a brief HPV-oriented program for adolescent. A limit of these two studies was the absence of information about SES. Wetzel and coll. (2007) evaluated the efficacy of a short counselling programme and observed an increase in knowledge. The intervention was effective in reducing the existing differences between black and white women and between those with Medicaid and those with private insurance. Other authors have tried to provide insights into effective communication about HPV, but with little supporting evidence (Tristram A et al. 2006; Dyson Y et al. 2010) and no mention of how to reduce SES inequalities.

Coverage of the target population

Longer intervals will influence the test population coverage because the definition of test coverage will change, but also because there may be an impact on women’s behaviours and attitude. There are no direct evidences, experimental or observational, in the literature on this point. Most of the literature is only speculative. Our systematic review retrieved 6 studies on coverage and HPV-based screening that treated social inequalities. Some authors speculated on the effect of longer intervals, and the two options are reported (Lazcano-Ponce et al 2011; Price RA et al. 2010; Bekkers RL et al. 2006; Tsu VD et al. 2009): longer intervals can facilitate achieving high population coverage; longer intervals may disrupt women’s habits and thus have detrimental effects on coverage. The second hypothesis is usually supposed to affect especially deprived women (Bekkers RL et al. 2006).

Many countries have a mixed model with opportunistic and organised screening existing together and sometimes competing for participation (PASSI 2011; Salo H et al. 2011). Only two documents mention the consequences on social inequalities of the interaction between spontaneous and organised screening in the era of HPV-based screening (Anttila A et al. 2013; Ronco G et al. 201). The introduction of HPV as primary screening test may have some consequences in this context and can surely change the inequality scenario: in the opportunistic setting, HPV will be much more expensive than Pap test, at least in the short term. If opportunistic screening offers the two options, less wealthy women will be pushed to undergo Pap test and richer ones HPV, regardless of what would be more appropriate. If the diffusion of HPV testing in the opportunistic setting were stronger and the offer of Pap almost disappeared, the coverage in less wealthy women would decrease or these women would be induced to
participate in organised screening programs. Finally, if the screening programs are reinforced by the introduction of HPV testing, it is likely that inequalities will decrease, as already observed in countries with well-established organised screening programs for cervical and breast cancer (Palencia L et al. 2010).

**Participation in screening program**

The proposal of a new test may influence attendance. Thirty-two studies were found, but only one trial (Giorgi Rossi P et al. 2011) and three intervention studies with historical controls (Price RA et al. 2010; Zorzi M et al. 2013; Confortini M et al. 2010) compared the participation in HPV-based vs. cytology-based screening program. The only trial (Giorgi Rossi P et al. 2011) focused on self-sampling, but used as control groups both standard invitation to have a Pap test at the clinic and an invitation to have an HPV test at the clinic. The sample size was small and the population was selected to be non-responder to the first invitation, but it found an 8%, non significant increase in participation. Data from pilot studies showed in most cases a higher participation in HPV-based screening than in Pap test-based screening. In particular, two Italian studies showed a 10% increase in coverage (Zorzi M et al. 2013; Confortini M et al. 2010). The increase was stronger in younger women, a group less covered than older women in Italy (Zorzi M et al. 2013). Another study (Price RA et al. 2010) found that after initial diffidence, Hispanic and black women were more likely to undergo HPV test than were white women. Some other papers reported the results of pilot or demonstration studies but without any term of comparison. Levinson and coll. (2013) found high acceptability in underserved Peruvian women, Marlow and coll. (2008) found that, in contrast to screening attendance, ethnicity plays an important role in HPV testing, and, finally, Philips and coll. (2006) report that adding HPV-based triage to the Pap program lowered the value of screening participation for only two women, whereas for the sample as a whole, it increased the average valuation by about 47 percent.

It is difficult to predict what impact the increase in participation will have on test coverage, but the increased costs in opportunistic screening and the increased appeal of programs offering the HPV test will probably increase participation in organised screening. Part of this increase will probably involve some women who are under- or never screened, which will result in a substantial reduction in inequality of access and in the burden of disease (Sundhedsstyrelsen et al. 2005).
Use of self-sampling devices

Self-sampling devices can be used to increase coverage and/or participation among non-responders. Twenty-two studies treated the effect of self-sampling on coverage or participation. Nine trials (Giorgi Rossi P et al. 2011; Gok M et al. 2010; Gok M et al. 2012a; Virtanen A et al. 2011; Szarewski A et al. 2011; Piana L et al.; Darlin L et al. 2013; Sancho-Garnier H et al. 2013; Wilkstrom I et al. 2011) and four reviews (Camilloni L et al. 2013; Sniders PJ et al. 2013; Schmeink CE et al. 2011; Stewart DE et al. 2007) found a positive effect of direct home mailing of the device, while other ways of offering the device are not effective (Giorgi Rossi P et al. 2011). Among studies reporting the acceptability of self-sampling among women, one showed that it was higher among married women and less accepted by some ethnic groups, such as Asians in the UK (Waller J et al. 2006) and another found (Anhang R et al. 2005) that it was higher among those with some or more college education (43% vs. 26%), and among those who were not Hispanic compared to Hispanic (49% vs. 28%). However, four studies found high acceptability also in the most hard-to-reach women (Zehbe I et al. 2011; Schmeink CE et al. 2011; Castle P et al. 2011; Dzuba IG et al. 2003). One of the main concerns in women performing self-sampling is not collecting an adequate sample (Giorgi Rossi P et al. 2011; Waller J et al. 2006; Forrest S et al. 2004; Howard M et al. 2009). This concern is stronger among Indian and African Caribbean women than among white British women (Forrest S et al. 2004). In particular, two trials in France conducted in two neighbourhoods with different socioeconomic levels (Piana L et al. 2011; Sancho-Garnier H et al. 2013) measured the difference in effectiveness of self-sampling in increasing coverage: they observed that the relative risk of having a test was higher in low socioeconomic status women but that the impact was limited in both contexts due to low participation and very low compliance to colposcopies in positive women. A study in the Netherlands (Gok M et al. 2012b), found that self-sampling was effective in increasing coverage among under-covered populations, but the response rate was higher in native-Dutch women and in women who already had had a previous Pap test. Another study, conducted in central Italy, found no effect of self-sampling in a rural area and a relevant effect in urban areas (Giorgi Rossi P et al. 2011), while a Swedish study found no difference in acceptance in different SES levels (Wilkstrom I et al. 2007). These studies, designed to test self-sampling as a tool to improve Pap test-based programs, suggest that the most deprived women, even in HPV-based programs, will have more difficulty accepting self-sampling, but an increase in compliance can be obtained in most of the socioeconomic groups.

Self-sampling devices can also be used to reduce sampling costs, though it could influence participation. Only one large trial in Mexico (Lazcano-Ponce E, et al. 2011) tested self-sampling as first
approach method and showed a lower participation for self-sampling than for Pap test when all the population was included in the analyses. If, however, we exclude women not found at home and to whom the self-sampling device was not mailed, the participation was over 98%. Such a result has the potential to eliminate any inequality in access to screening, providing we have complete lists of resident women with updated and accurate addresses.

**Compliance to screening protocols**

Nine papers treated the differences in compliance with respect to HPV-related protocols. Compliance to a 5-year interval after HPV negative test may be low for women used to having a Pap test every year (Ashok M et al. 2012), thereby increasing spontaneous opportunistic over-screening. No published data were found about compliance to the recommended interval after HPV. Previous studies found an association between intervals shorter than recommended and high socioeconomic status women (Maissener H I et al. 2010; ISTAT 2006). Consequently, if over-screening increases, the phenomenon will probably be less relevant for deprived women.

Non-compliance with the recommendation to repeat test after 1-year (or six months), both in terms of under- and over-screening, may be influenced by socioeconomic status. It has been observed that women have an overwhelming preference for immediate colposcopy rather than continued surveillance for persistent HPV (Waller J et al. 2007). Cultural background can influence the compliance to protocol and increase or decrease induced anxiety when a woman receives a result of HPV positivity and there is no immediate referral to further assessment.

Some authors considered the implication of effective communication of the test results on compliance to one-year follow up (Confortini M et al. 2010, Ronco G et al. 2012). The implications differ depending on whether it is necessary to invite the women back to collect a cytologic sample or whether the sampling method allows reflex cytology in to be performed (a liquid-based cytology or a double sampling taken at the same moment). In the first case, high compliance is needed to obtain the second sample. If the Pap test is negative, women who are HPV positive and Pap test negative must be reassured about waiting one year before repeating the test so as to avoid unnecessary colposcopies or other evaluations during that period. In the case of a reflex cytology test, we can give the HPV and cytology results at the same time, leaving only the problem of reassuring women for the one-year follow up. Compliance to protocols varied dramatically among trials and pilot studies results, with some programs obtaining more than 85% without any particular interventions (Zorzi M et al. 2013) and other pilot studies (Confortini M et al. 2010) and trials with relevant loss to follow up in HPV+ women.
(Kitchener H et al. 2009; Bulkmann NW et al. 2007) when colposcopy was delayed. In some cases there was evidence of overscreening (Confortini M et al. 2010), but there are no data on SES differences. In a non-randomized study, a brief phone counselling at the moment of HPV positivity strongly increased the compliance (65% vs. 35%) to one-year follow up (Confortini M et al. 2010). All the problems related to compliance to recommended protocols are more critical when a strong opportunistic offer is present (Anttila A et al. 2013; Martin-Moreno et al. 2012), in particular when there is risk of overuse of screening test (i.e. shorter intervals or extra Pap test in HPV-negative women) and of evaluations (i.e. extra colposcopies in HPV+ cytology-negative women). In fact, in opportunistic screening gynaecologists usually recommend a yearly Pap test and women are used to shorter intervals than that recommended by organized screening. In some focus groups (Cogo C et al. 2006; Iossa A et al. 2010), a certain diffidence against longer intervals emerged when proposed by the public health system because it was perceived as a budget cut rather than a measure to avoid overtreatment (Sawaya GF et al. 2010). Even if this sort of scepticism may be present in all cultural and economic strata of society, the effect on compliance will probably be greater among women with higher SES because they undergo regular gynaecological exams more frequently than do women with low SES.

The only way to reduce negative interactions between organized and opportunistic screening during the HPV screening implementation is to reduce discrepancies between organised program protocols and the attitudes/recommendations of gynaecologists and general practitioners working outside the program, be they public or private providers. How to achieve this is beyond of the scope of this paper, but education and participation in the definition of local protocols, within the limits imposed by the evidence, are necessary steps in the process (Formoso G et al. 2001; Grimshaw JM et al. 2004).

Communication of positive results and related anxiety

Finally, the communication of HPV infection positivity poses new problems combining the anxiety and the implications related to a sexually transmitted disease with that related to cancer (Maissi E et al. 2004; Maissi E et al. 2005). We found 13 papers on the communication of positive results and how a woman’s socioeconomic status can affect how she receives it.

Previous systematic review (Ronco G et al. 2012; Arbyn M et al. 2008; Anhang R et al. 2004a) found that communicating the result of an abnormal Pap smear may induce anxiety, fear of malignancy, difficulties in sexual intercourse, a different perception of the body, and fear of becoming infertile (Lerman C et al. 1991; Campion MJ et al. 1988; Basen-Engquist K et al. 2004; Bell S et al. 1995).
Furthermore, some women reported fear of pain caused by colposcopy and treatment, which may cause loss to follow up (Basen-Engquist K et al. 2004). One paper shows that the anxiety induced by positive Pap test results (Drolet M et al. 2011) was stronger in women with low socioeconomic status. Indeed, we can suppose that many of the feelings related to a positive result are determined by the woman’s knowledge and ability to understand the midwife’s or gynaecologist’s indications, which is almost certainly associated with her educational level. All these concerns are also valid in HPV-based screening and may be even more intense given the higher proportion of positive women (McCaffery 2004). Furthermore, there are concerns that are unique to HPV-based screening: since this test explicitly targets a sexually transmitted virus, positivity may have an impact on sexual behaviours and relationships (McCaffery K et al. 2004; McCaffery K et al. 2003). This concern has been shown to be higher in low education level women and non-white ethnic groups in the UK (Waller J et al. 2009), and more in general, to women’s social status (married vs unmarried), sexual history (number of partners), cultural background (sexual norms and practices), and knowledge and understanding of the link between HPV and cancer (McCaffery K et al. 2006). Several studies dealing with this found that current and past relationships, cultural norms concerning sexual habits, and knowledge of HPV and cervical cancer were possible modifiers of the psychological response to a positive result (McCaffery K et al. 2004). Two studies using focus groups to evaluate the health education material and response letters of a pilot screening program found that the women asked for shorter texts and simpler wording; the greatest concerns were related to the difficulty in understanding the real risk of cancer (Iossa A et al. 2010; Goldsmith MR et al. 2007). Finally, Waller et al. (2005) concluded that the way in which information is presented to women may be crucial in minimizing the negative psychological impact of testing positive and ensuring that participation in screening remains high.

Eight studies analyzed the health information needs of women undergoing an HPV test and in particular, of those receiving a result of positivity (Anhang R et al. 2004b; Kahn JA et al. 2007; Goldsmith MR et al. 2007; McCaffery K et al. 2005; McCree DH et al. 2006; Perrin KK et al. 2006; Rosen NO et al. 2009; Sharpe PA et al. 2005). Only one, based on Pap test experience, reports the results of different communication strategies. However, given the low number of participants (20 women), the authors could not determine whether effectiveness was associated with SES. Women questioned whether communicating results by letter would violate their privacy and generally preferred receiving a phone call because it permits immediate clarification, thereby reducing anxiety. The most preferred mode was face-to-face communication, for negative and positive results alike. In fact, they were worried that a differentiated mode of communication (letter for negative results and face-to-face
for positive results) would increase their anxiety because the amount of time that elapsed from the date of the appointment would implicitly mean a positive result, to be confirmed or not during the counseling itself (McCaffery K et al. 2005).

Obviously, a phone call and face-to-face communication make it possible to modulate the message according to the woman’s coping, linguistic abilities, and educational level. However, there are two main obstacles to implementing face-to-face communication: it is very time-consuming and, to avoid increasing anxiety, it should be done for both negative and positive results.

**Vaccine and screening interaction**

One of the most treated topics in the literature was the interaction between vaccination and screening, with 10 papers directly reporting data on this topic. Two main points were treated: 1) the effect of vaccination on women’s attitude to screening and consequently on test coverage (Brotherton JM et al. 2012; Kulasingam SL et al. 2007; Bauch CT et al. 2010; Goldhaber-Fiebert JD et al. 2008; Hilton S et al. 2011; Branković I et al. 2013), the hypothesis is that being vaccinated could change future participation in screening (usually the authors suggest a decrease - Kulasingam SL et al. 2007; Bauch CT et al. 2010); 2) the association between vaccination and future screening attitude (Mather T et al. 2012; Marlow LA et al. 2008; Lefevere E et al. 2011; Steens A et al. 2013; Chao C et al. 2009), i.e. those girls who do not do the vaccination now are probably those who will not participate in screening in the future. The consequence is that the impact on cervical cancer screening of vaccinated cohorts will be minimal because most cancers will occur in women not vaccinated and not screened (Goldhaber-Fiebert JD et al. 2007). These two phenomena are not typical of the HPV-based screening and most of the literature considered the relation between vaccination and Pap test use.

The first point has been treated by Brotherton and colleagues, with interviews to girls to whom vaccination had been proposed: only 8% said that HPV vaccine could have a negative effect on their future screening habits.

As for the second point, two study designs have been used: attitude interviews to vaccinated and unvaccinated girls already in or close to the screening target age (Mather T et al. 2012; Mehta NR et al. 2012); for younger girls, the association between the mother’s Pap test use and the daughter’s vaccination state (Marlow LA et al. 2008; Steens A et al. 2013; Lefevere E et al. 2011). The results are mixed: two studies (Mather T et al. 2012; Marlow LA et al. 2008) found no association while the others found a strong association between vaccination and screening (Metha T et al. 2012) or between mother’s participation in screening and her daughter’s being vaccinated (Steens A et al. 2013; Lefevere
E et al. 2011; Chao C et al. 2009).

None of the studies hypothesised how the introduction of HPV test might modify these phenomena. Only the study by Marlow and colleagues explicitly measured attitudes to HPV testing. The general opinion is that HPV should be the primary screening test in vaccinated cohorts (Franco EL et al. 2006) and research on vaccine and screening interaction should be directed to define the best screening algorithms for vaccinated women.

**Conclusions**

Since equity in access is one of the main objectives of organised screening programs, the introduction of HPV test may be a way to increase population coverage and thus finally include some of the hard-to-reach women. Interactions with spontaneous screening may increase overscreening and inappropriate use of evaluation tests although this phenomenon is likely to be more relevant among women with higher socioeconomic status.

There remain, however, problems concerning how to communicate positive results, control induced anxiety, and reduce non-compliance to protocols, which may augment existing inequalities if particular attention is not paid to effective communication.
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Competing Interests
PGR is the principal investigator of a project sponsored by the Italian Ministri of Health and data owner. For this project, PGR in contact with ROCHE DIAGNOSTICS, HOLOGIC-GEN Probe, QUIAGEN, ABBOTT, for tests at reduced price or free of cost. All other authors have no conflicts of interest

Figure Legends
Figure 1. Putative screening algorithm according to the up-coming European Guidelines (Ronco G. et al. 2012) and critical points related to social inequalities. Along the pathways depicted by the screening algorithm flowchart, the callouts explain where critical points for increasing or decreasing social inequalities have been identified or hypothesized. The colour-code of the callouts corresponds to the main topics, as reported in Table 1 and figure 2, to which the critical point refers: in blue, points related to test coverage of the target population, in yellow points related to participation in screening programs, in green, points related to compliance with screening protocols, in orange points related with communication of positive results and anxiety.

Figure 2. Flowchart of the systematic search. The colour code of the main topics is the same as reported in figure 1.
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The positive results for HPV infection, a sexually transmitted disease, may have an impact on sexual behaviours and relationships. Cultural background can modify the effects.

Invitation to a new test, different from Pap test, may influence the participation in screening programme. The effect on participation may be different according to socioeconomic status, cultural background, and screening status.

Self-sampling device can be used to reduce sampling costs. Participation in self-sampling may be lower in uneducated women.

Self-sampling device can be used to reduce non-attendance to screening. Effectiveness in increasing coverage in hard-to-reach populations is under debate.

Access to opportunistic HPV testing has been limited by the high cost of the test in private laboratory.

Non-compliance with recommendation to early re-screening, both in terms of under- and overscreening, may be influenced by socioeconomic status.

Cultural background can influence the compliance to protocol and influence the induced anxiety when a woman receives an answer of HPV positivity and there is no referral to further assessment.

5 yr or more

HPV test

Sampling allowing both molecular and morphological tests

positive

Opportunistic screening

no

Participation

Introduction to screening

Self-sampling device

dashed line

negative

HPV test

negative

Cytology

positive

Colposcopy

Early re-screening