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Invited Commentary

The improbable plunge. What facts refute reasons to expect that the effectiveness of HPV vaccination programs to prevent cervical cancer could be low?

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There are powerful reasons to hope, believe, expect or predict that universal vaccination with HPV vaccines of teenage girls in Western countries will in some 30-60 years prevent many – or even most – cases of cervical cancer (Baden et al., 2007; Bosch et al., 2008; Haug, 2008). Regulatory decisions on HPV vaccines and political decisions on HPV immunization programs taken during the past few years do have a scientific basis. Of course – science being a quintessentially human activity (Gould, 2004) – not all such reasons are purely scientific. Some are political and ideological, which is inevitable, and not necessarily detrimental for public interests. Marketing of HPV vaccines is a scientific success for academia and industry. It may also be a deserved commercial and economic success. All this is positive. The mid- and long-term implications for public health of routine vaccination are less clear. For instance, little evidence seems to be available to assess whether there will be an increased incidence of precancerous cervical lesions caused by HPV types other than HPV-16 and HPV-18 (Baden et al., 2007; Haug, 2008; Lippman et al., 2007; Minnesota Department of Health, 2008; Porta et al., 2008). Immunity may wane with increasing age and exposure to different HPV types, and the duration of protection conferred by current vaccines is unknown beyond some 5 to 7 years. The number of girls aged 9–15 that took part in phase III clinical trials is rather small (Lippman et al., 2007). Valid, population-based studies on HPV genotype distribution are lacking in many countries, and the available data reinforce doubts on the public health impact of vaccines currently administered (Wheeler et al., 2009). In many states in the US less than 25% of candidate adolescents have received all three doses, but data are still scant (Jain et al., 2009; Markowitz et al., 2009; Tuma, 2009). Even in Western countries, and certainly in the US, about 60% or more of all cervical cancer cases occur in women from the lower social classes, who have low or no access to quality screening services (Jain et al., 2009). Since women not screened are also more likely not to get vaccinated, the impact of vaccination programs will be less than promised, and health inequalities may once again increase.

It is striking – or is it not? – that statements on the promise of HPV vaccines are more common in the academic, professional and lay media than plain statements like the following (from an editorial in the *New England Journal of Medicine*):

"Despite great expectations and promising results of clinical trials, we still lack sufficient evidence of an effective vaccine against cervical cancer.… The overall effect of the vaccines on cervical cancer remains unknown.… The real impact of HPV vaccination on cervical cancer will not be observable for decades." (Haug, 2008)

Thus, the debate about the extent to which the available evidence supports the decisions that have been made to date is alive. Such decisions strongly reflect or result from the surrounding social context we scientists and health professionals lived in when certain marketing strategies and political decisions were taken over 5 years ago, such as which type of HPV vaccine to include (and pay for) in national immunization programs. Consider under what rules the economy functioned *circa* 2004 and earlier on (Porta et al., 2007). The remembrance is not difficult because we are now suffering the ensuing economic debacle. It would be difficult to argue that such financial and commercial rules did not affect at all the scientific and political assessment –in full effervescence a few years ago– of the evidence on the potential effectiveness of HPV universal vaccination programs to decrease mortality from cervical cancer. Naturally, many components of such analyses have to do with *knowledge construction* and with the sociology of scientific knowledge (Porta, 2008); these are approaches to the understanding of science that analyze how knowledge is created, and which identify strategies that scientists, technicians, companies and other users of science products employ in their work, discursive fact production, fact construction across epistemic communities,

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"epistemic machineries" (i.e., machineries of knowledge production), and social mechanisms of consensus formation (Merz, 2005).

Perhaps the full effects of current vaccination policies upon cervical cancer incidence and mortality will be established around 2040-2070. Few of us will be present to assess such results, and certainly very few, if any, of the politicians and industry professionals who championed vaccination. Most likely, current HPV vaccines will be obsolete before that time (Tuma, 2009). Much more importantly: the time dimension (e.g., the lag-time between vaccination and prevention of the target disease) has seldom been explained by scientists, medical organizations, industry, and health policy-makers when we have spoken to the general public through the mass media (Dören, in press; Dören et al., 2009; Porta et al., 2008). This is in sharp contrast to the common emphasis on the huge burden that cervical cancer supposedly poses everywhere. It is a clear example of how social agendas are shaped, putative risks and benefits ('knowledge') are constructed, and societal actors are persuaded. Also, the relationship between vaccination against HPV and prevention of cervical cancer has often been assumed to be as simple, acute in time, and scientifically proven as the relationship between vaccination and eradication of communicable diseases like polio or measles. Yet, clinical trials of HPV vaccines have had a rather limited duration with respect to the lifetime risk of cervical cancer—which is a major reason why the long-term, true effectiveness of HPV vaccines to substantially decrease the population burden of cervical cancer and related pathologies is still unproven (Baden et al., 2007; Haug, 2008; Lippman et al., 2007; Markowitz et al., 2009; Minnesota Department of Health, 2008; Porta et al., 2008).

Two other related and relevant phenomena show the influence of the economic and cultural values that prevailed before the present economic and financial crisis, and that still largely prevail. First, the scientific value of the technological *vaccine product* (which many of us praise (Baden et al., 2007; Dören et al., 2009; Haug, 2008; Lippman et al., 2007; Minnesota Department of Health, 2008; Morabia, 2009; Porta et al., 2007)) has been commonly transplanted and equated with the societal value of *vaccination programs*. Second, the HPV vaccine, a fundamental public health tool, has been extensively "commodified", i.e., presented and sold as a commodity, an object of trade and individual consumption. Another result of the same underlying influences has been a systematic underestimation of vaccine costs and of the additional resources needed to implement immunization programs of high coverage and quality. Let us also remember that countries that would most need an effective cervical cancer vaccine are the ones without screening programs, without the human and economic resources to spend on primary and secondary prevention, and with the worst economic and democratic environments. Even in countries with a low incidence of cervical cancer (i.e., with no public health crisis or emergency due to the disease) authorities adopted the decision to universally vaccinate girls with unusual expediency (de Kok et al., 2008; Dören et al., 2009; Lippman et al., 2007; Porta et al., 2007).

Enormous amounts of money appear to have been spent on "public relations efforts" to promote pro-vaccine decisions (Boseley, 2007; Udesky, 2007; Wynia, 2007). Large areas of opacity exist in such campaigns, with troubling questions concerning the roles played by some sectors of the biomedical industry, scientific institutions, government and medical organizations, and the mass media (Márquez-Calderón et al., 2009; Wynia, 2007). Certainly, disclosure of interests has been occasionally practiced; notably, by epidemiologists publishing in academic journals (de Sanjosé et al., 2007). Yet the whole process suggests that disclosure of interests in academic journals, essential as it is, does not suffice to properly sort out scientific, clinical, public health, commercial and political interests. Another, no less relevant type of opacity has afflicted assumptions in some models assessing cost-effectiveness (e.g., untested assumptions on duration of vaccine protection) (Puig-Junoy and González López-Valcárcel, 2009). In the special section on HPV readers will also find an innovative national strategic framework to integrate and evaluate the primary and secondary prevention of cervical cancer (Howlett et al., 2009); it tries to take into account the fact that given the long time from HPV infection to cancer and the recommended early age for immunization, it will be decades before the full benefit of the vaccine will be assessed for prevention of HPV-related cancers.

Two additional drawbacks of the scientifically unfounded part of efforts to promote universal HPV vaccination deserve more attention and research. First, the weakening of public confidence in current immunization programs: suspicion toward reasons behind HPV vaccination programs affects other immunization programs that have a strong evidence basis. Second, the *HPV-ization* of the lives of many women and men (Porta et al., 2008): in some countries there have been vast exaggerations of the risks conveyed by infections with HPV; yet HPV infections are not *per se* a disease. Such misrepresentations are regrettable attempts to further medicalize (*HPV-ize*) the lives of millions of citizens. Fortunately, in many instances HPV infection has been accurately portrayed as often benign, slow, naturally reversible, and amenable to control with non-aggressive measures (Allen et al., 2009; Howlett et al., 2009; Dören, in press; Lippman, 2008; Porta et al., 2008; Waller et al., 2009; Ziarnowski et al., 2009). A critical assessment of vaccination policies should also strengthen analyses of screening programs; another of the articles in the special section on HPV reveals substantial overconsumption of such programs, with limited health benefits (Arbyn et al., 2009). Structural reduction of overuse and extension of screening coverage is warranted in many countries.

We may pragmatically accept or disregard as habitual the commercial influences, even if we believe that mandatory universal vaccination is a highly valuable strategy that requires huge public trust and sustained coherence to maintain such confidence (Wynia, 2007). Non-scientific influences may be inevitable, may have positive sides, but may not actually be that influential. Nevertheless, the core issue remains: is there enough scientific knowledge in support of universal HPV vaccination programs to prevent cervical cancer?

Indeed, *there are* some powerful *scientific* reasons to expect that universal HPV vaccination will in a few decades prevent a significant part of the population burden of cervical cancer and related pathologies (including, to a much lesser extent, other HPV-related cancers such as cancer of the penis, anus, vagina, vulva, and some oral cancers). All sorts of reasons in favor have been explained extensively (Baden et al., 2007; Lippman et al., 2007; Minnesota Department of Health, 2008). In addition to those reasons, the complex decision processes of regulatory agencies are another reason why it may be wrong to reason as follows:

- clinical trials have been much too brief and restrictive to assess the effectiveness of HPV vaccines to prevent cervical cancer and the societal impact of HPV vaccination programs with respect to other policy alternatives;
- many times in medicine and public health facts have refuted scientifically sound expectations, i.e., biological, clinical and epidemiologic evidence on mechanisms and etiopathogenic processes have not been followed by the expected outcomes of interventions of true clinical and social significance;
- even for clinical conditions affecting sick individuals that seek medical care and can be treated on a one-to-one basis (*e.g.*, prescription drugs), pragmatic clinical trials are usually required to prove that the intervention is effective for the specific clinical condition, not just for an intermediate endpoint or surrogate biological marker;