Comment on:

SCHIM VAN DER LOEFF et al. (2019):

„Should female sex workers be offered HPV vaccination?“

In May 2019, the first ever article about the pros and cons of HPV vaccination of FSWs in a peer-reviewed scientific journal was published in „Human Vaccines & Immunotherapeutics“ (15; 7 - 8: 1544 – 1548), entitled:

„Should female sex workers be offered HPV vaccination?“

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The article of SCHIM VAN DER LOEFF et al. is the first paper about the question of HPV vaccination of FSWs in a peer-reviewed journal. There were some former papers with respect to the implementation of HPV vaccination for FSWs, e.g. about a trial in Lima/Peru (BROWN et al. 2011, 2012, 2013), but they didn't consider in detail the pros and cons of such vaccination and the question whether vaccination is still effective at all when it is administered to a highly pre-exposed adult female population like FSWs. The article of SCHIM VAN DER LOEFF is restricted to female sex workers; however, many aspects are applicable to MSWs and transgender SWs as well.

SCHIM VAN DER LOEFF et al. note the high HPV risks of FSWs, the limited protection of condoms, the limited use of condoms (in part depending on the sex work setting) and the young age (~ 50 % < 26 years) of many FSWs.

The authors mention the following arguments in favor of vaccination:

● high risks of HPV infection, the precursors of cervical cancer, and thus cervical cancer in FSWs; higher risk for anogenital warts and – possibly/probably – anogenital cancers
● unlikeliness that FSWs are already vaccinated against HPV
● the excellent immunogenicity of the vaccine even in women who were previously exposed to HPV types from the vaccine
● recurrence rates after surgical treatment of CIN are lower in vaccinated than in non-vaccinated women, so even infected FSW may profit from vaccination

● the efficacy of the vaccine in mid-adult women (26 – 45 years) against persistent infections and CIN2+, as demonstrated by several RCTs (randomized control trials), at least if the women are not infected with the HPV types from the vaccine at the time of vaccination. Moreover, seropositivity against HPV 16/18 as a marker for a previous infection by these HPV types doesn't seem to impair the efficacy of vaccination a lot.
● FSWs who may be currently infected with one or two HPV types from the vaccine may still profit from protection against the other HPV types of the vaccine. For example, 64 % of FSWs in Amsterdam are "naïve" with regard to HPV 16 (PCR-negative and sero-negative), and these percentages are even higher for other hrHPV types from the vaccine.
● protection of clients, their other sexual partners, and herd immunity with effects on the general population. Vaccine-induced neutralizing antibodies on the surface of the female genital tract prevent further transmission to clients (even in FSWs who are infected). The authors calculated that about 500.000 HPV transmissions can be prevented each year, if all ~ 5000 FSWs in Amsterdam are vaccinated.

The authors note the following arguments against vaccination (discussed in detail below):

● the A5298 trial, which showed no statistically significant efficacy of Gardasil vaccination against persistent anal infections in a heavily pre-exposed adult cohort, dominated by HIV-positive MSM
● women who already cleared a HPV infection may be protected by natural immunity and may thus be able to clear a reinfection even without being vaccinated in the meantime
● not all HPV infections in women result in serum antibodies, so there may be women/FSWs presumed to be HPV-naïve (PCR-negative and seronegative) who were in fact infected in the past and cleared this infection without leaving detectable titres of antibodies, so the percentage of "truly" naïve FSW (64 % for HPV 16 in Amsterdam) may be overestimated
● the unresolved role of latency. It is not expected that vaccine-induced antibodies are able to clear latent infections (the virus is intracellular and antibodies cannot bind to it). It is unknown whether vaccination can suppress recrudescence of latent infections.
● a case-control study of CIN 2+ prevalence in vaccinated vs. non-vaccinated women which investigated the role of different doses of Gardasil ("1 or 2" versus "3 and more") and ages at the time of the first vaccine dose showed no *(strictly speaking: only a small and insignificant*) effect in those who got the first dose at an age of 21 years or beyond (SILVERBERG et at 2018).

In their discussion, SCHIM VAN DER LOEFF et al. pointed out that three different aspects of HPV vaccination of FSWs have to be considered: the impact on an individual FSW, on the population of FSWs, and on the general population. *"There are no clear-cut data about the effectiveness of HPV vaccination of highly, pre-exposed women, while indirect evidence suggests some degree of effectiveness"* (SCHIM VAN DER LOEFF, p. 1546). Furthermore, the authors state that HPV vaccination of FSWs *"could provide health benefits for the (male and female) population at large."*

On an individual base, they pointed out *"not all SW are the same",* and in individual cases the balance between pros and cons may favor vaccination, for example in women who

recently started sex work or plan to do so in the future and who had little vaginal/anal sexual experience in the past *("then HPV vaccination should certainly be recommended").*

The authors see the need for more data and more research, including studies on the long-term effect of vaccination in highly pre-exposed women, but acknowledge that a RCT in a SW population to study the effectiveness of the vaccine in this group would be difficult. The article concludes with the sentence: *"In individual cases, HPV vaccination of SW may be recommended".*

Comment:

The article is very interesting and important, because it is the first article which discusses the pros and cons of HPV vaccination of FSWs in a peer-reviewed scientific journal. It took 13 years after the implementation of the HPV vaccine until the first article on this subject was published. This means a big progress in this field and a base for further discussion and research.

I agree with all of the content of the paper. This is not a big surprise, because we used nearly completely the same literature. I especially agree with the three different perspectives on the subject in the discussion: (i) that HPV vaccination of as many FSWs as possible has a favorable effect on the population at large, the clients of FSWs and the private partners of the clients and FSWs (in the sense of herd immunity), (ii) that not all FSWs are the same and that there are FSWs to whom FSW vaccination should be (strongly) recommended (need for balance of pros and cons for each individual FSW), and (iii) that there is currently no evidence to recommend HPV vaccination to all FSWs in general, furthermore (iv) that there is a lack of *direct* evidence for or against HPV vaccination of FSWs because there are no such studies in the FSW population, and (v) that it is very difficult and (depending on the type of trial, e.g. RCT) even impossible to carry out HPV vaccination trials within the FSW population, at least as far as the effectiveness of the vaccine for FSWs is concerned (of course one can carry out trials with regard to the acceptance of the vaccine by FSWs and similar subjects, see BROWN et al.).

Therefore it makes no sense to wait until such studies are published (because this will probably never happen), and one has to weigh the *available evidence* pro or contra vaccination of an individual FSW from other studies or study populations. So the evidence on which one has to rely is only *the best available evidence* (this means: indirect evidence), *not the best (theoretically) possible evidence*. It makes no sense to wait until the (theoretically) possible best (direct) evidence is available, while in the meantime many FSWs are exposed to HPV risks and disease burden which can be reduced (at least in part) by vaccination.

Oral/oropharyngeal risks

However, there is an additional important aspect which is not mentioned in the SCHIM VAN DER LOEFF et al. article and which may influence the balancing of pros and cons in a lot of individual cases.

It is well established meanwhile that unprotected oral sex may result in oral/oropharyngeal HPV contamination and infection. If this infection becomes persistent, it may result in oral/oropharyngeal cancer (*abbr.:* OOPC; mostly tonsils, base of the tongue) after many years or decades, and there is no secondary prevention/early detection method available for these cancers in the moment (contrary to cervical cancer). It is well established now (with several dozens of original and review papers), (i) that oral sex (fellatio and cunnilingus; the role of tongue kissing is still unclear and at most very small) is the dominant source of HRHPV/HPV16 infection in the mouth and oropharynx, (ii) that the prevalence of oral/oropharyngeal HRHPV is strongly correlated with the number of oral sex partners (more strongly with this number in the last 1 – 2 years than the lifetime number due to the clearance of most of these infections), and (iii) that the risk of HPV-associated oral/oropharyngeal cancer (OOPC) correlates with the lifetime number of oral sex partners and the amount of lifetime oral sex experience. (Oral LRHPV correlates less strongly with oral sex practices; studies which look for "all oral HPV types together" and which are not restricted to HRHPV or HPV16 may thus underestimate the role of oral sex with regard to HPV infections of clinical significance, or may even fail to find results of statistical significance). For example, in unvaccinated men and women from the NHANES population (US) who had oral sex within the last 12 months, the oral prevalence of HPV16 and/or 18 was found to be 0.4 % in persons with 1 lifetime oral sex partner, 1.2 % in persons with 2 – 24 lifetime oral sex partners, but 6.5 % in persons with more than 24 lifetime oral sex partners (GUPTA et al. 2019; combined for men and women; ~ 57 % women).

There is a strong and continuing rise in the incidence of HPV-associated OOPC since a few decades in North America and Europe. The most impressive data come from Scandinavia (especially Sweden) and US.

However, because Cancer Registry data don't distinguish between HRHPV-positive und HRHPV-negative OOPC at the same anatomical site, the rise in HPV-associated OOPC can be easily overlooked when working with Cancer Registry data, because at the same time, the incidence of HRHPV-negative OOPC cases, mainly (nearly all) caused by smoking, is decreasing, since smoking habits decrease since many years in the general population in developed countries. The combined effect (rise of HRHPV-associated OOPC, but decrease of smoking-induced cancers) may result in a stagnation of OOPC incidence, and so one can easily miss that there is a problem with HPV-associated OOPC. As Aimee Kreimer from the National Cancer Institute (NCI) (US) pointed out in some of her papers, the incidence of HPV-associated OOPCs (combined for men and women) will exceed the number of incident cervical cancers in the in the US very soon. (For review of the most recent knowledge in the field of epidemiology see SHEWALE and GILLISON 2019).

HPV-associated OOPCs mostly affect the oropharynx and especially tonsils and the base of the tongue (i.e. the epithelium in context with lymphatic tissue); however, they may also occur at many different sites in the oral cavity, though the relative portion of HPV-associated

cancers among all cancers of the oral cavity is smaller than it is in the oropharynx (where HPV is the dominant cause meanwhile), and the combination of smoking and heavy alcohol drinking is still the most important cause for cancers of the oral cavity.

HRHPV and smoking(+ alcohol) utilize different molecularbiological pathways to induce cancer in the oral cavity and oropharynx. This means that persistent HRHPV infection in the oral cavity/oropharynx is not solely a carcinogenic cofactor (like alcohol) to smoking; HRHPV, especially HPV 16, itself is a primary carcinogen in the mouth and oropharynx, and so even nonsmokers/nondrinkers may get this cancer type though it is very unlikely for them to get HRHPV-free cancers at these sites, especially in the oropharynx.

In US it is an often cited observation, cited in many papers about HRHPV-associated oral infections and cancers in mouth and oropharynx, that these HPV-associated OOPCs are found not so rarely in younger, non-smoking, socially/financially better situated white men compared to smoking/alcohol-induced cancers which are more often found in older, socially more deprived, heavily smoking and drinking men. Women are affected too, but less often than men.

Nevertheless, smoking is a cocarcinogen on the HRHPV-associated pathway because it reduces the natural immunity against HPV and thus delays or impedes clearance and promotes the progression towards cancer. Smoking also enhances viral shedding on the infected mucosal site and thus enhances infectiousness and the risk for sexual partners. So smoking is in fact an additional risk factor also for HPV-associated OOPCs, and smokers are found to have significantly higher oral HPV 16/18 prevalences (e.g., GUPTA et al. 2019), but not on its own (smoking-specific) pathway, but smoking strengthens the HPV-associated pathway to cancer.

Both fellatio and cunnilingus may result in oral/oropharyngeal HPV contamination and infection. However, the pro-act risk of cunnilingus seems to be higher than that of fellatio because of a higher viral load on the female genital mucosa and in genital secretions compared to the surface of the skin and mucosa of the penis. This may explain the higher prevalence of oral/oropharyngeal HRHPV infections in healthy men as well as the higher percentage of men among all patients with HRHPV-associated OOPCs compared to women. Furthermore, due to genital HPV contamination or infection earlier in life, the natural immunity against oral/oropharyngeal infections seems to work better in women than in men, thus explaining in part the differences in the prevalence of oral/oropharyngeal HRHPV infections and OOPCs between men and women (contrary to genital contaminations or infections in women, penile infections don't seem to induce a clinically relevant degree of humoral or antibody-mediated natural immunity, and they rarely induce the production of antibodies. This may also explain why penile HRHPV prevalence shows a tendency to rise with increasing age, whereas cervical HRHPV prevalence is decreasing; e.g. BROUWER et al. 2019).

However, even women are at risk of HPV-associated OOPCs, and smoking seems to impair the effectiveness of naturally acquired immunity from former genital contaminations or infections. Thus oral/oropharyngeal HRHPV and OOPC is not restricted to men who practiced unprotected oral sex; it also affects women with a risky sexual lifestyle, but with

higher risks for smoking women due to impaired natural immunity (which nonsmoking women may gather as a consequence of their sexual lifestyle).

Since unprotected oral sex is an important service in sex work, maybe the most important in some countries or sex work settings or for some (or many?) individual FSWs (though it is prohibited by law now in Germany as far as fellatio on men is concerned, but unprotected cunnilingus is not forbidden), the oral risks have also to be considered in the individual balance for the recommendation for (or against) HPV vaccination for an individual FSW (or MSW). Contrary to cervical cancer, there is currently no secondary prevention/early detection program available for HPV-associated OOPC or precancer, what leaves vaccination as the only way of prevention (apart from consistently protected oral sex; see GUPTA et al. 2019).

Though it is forbidden now in Germany, and the fine for the client may be (theoretically) as much as 50.000 Euro, unprotected fellatio is still practiced frequently. Some FSWs welcome this aspect of the law (Prostituiertenschutzgesetz) because it offers to them a good reason to decline unprotected fellatio. However, many FSWs have plausible reasons why they continue to practice unprotected fellatio, and why some of them really *like* to do so. These reasons are discussed in a German forum-based paper and called "the oral sex dilemma".

Furthermore, in settings where FSWs don't work alone, many FSWs like to perform threesomes and/or lesbian games/actions with colleagues. Due to the high prevalence of HRHPV on the genital mucosa of unvaccinated FSWs, and the higher viral shedding on female genital mucosa compared to the penis of infected men (and even more in smokers), this practice (cunnilingus on colleagues) results in a higher per-act risk of acquiring oral/oropharyngeal HRHPV compared to fellatio on male clients.

As a consequence, FSWs who practice unprotected oral sex with clients (and even more, when they practice cunnilingus on colleagues) are without doubt highly exposed to oral/oropharyngeal HRHPV contaminations and they are one of the subpopulations with the highest risk for incident and persistent oral/oropharyngeal HRHPV infections, and, as a consequence, HPV-associated OOPC. Among all women, these FSWs are probably the group with the highest risk at all, especially if they are smokers.

Fortunately nearly all HRHPV-associated OOPCs are caused by HPV 16, with a small contribution of HPV 18; the effect of all other HPV types together on OOPC is negligible, at least in Europe and North America. Thus even the bivalent vaccine covers nearly completely the spectrum of HRHPV types which are relevant in the mouth and oropharynx (much more specifically than at the cervix), though the nonavalent vaccine offers a small advantage since warts of the anogenital type may also occur in the mouth (though rarely), and a few cases of OOPC seem to be associated with HPV 6.

There are no studies which prove that (former) FSWs have a higher risk of HPV-associated OOPC. Such studies would be unpractical due to the long time (1 – >3 decades) between HPV infection and symptomatic OOPC, so most affected women would have stopped working in the sex industry a long time before cancer diagnosis. And many former FSWs repress their former involvement in sex work psychologically after they stopped it, and therefore won't disclose it many years or decades later when cancer is diagnosed. Thus we

have only *indirect evidence* that FSWs who practice unprotected oral sex will have a higher risk of HPV-associated OOPC many years later (though HPV-16-E6-antibodies might be a proxy for that risk, because they occur many years before cancer diagnosis, but probably more reliably in non-smokers than in smokers), but this indirect evidence is strong due to the high number of studies and papers which demonstrated the association between oral sex experience (e.g., number of oral sex partners), oral HPV 16 infection, and HPV-associated OOPC.

Though FSWs who practice unprotected oral sex are heavily exposed to risks of oral HPV contamination, their oral/oropharyngeal prevalence of HPV 16 is much smaller than at the cervix or anus (as far as one knows in the moment). There are only a few studies with respect to oral HPV 16 prevalence in FSWs (and no studies concerning persistent oral infections in FSWs), and it was found to be about 2 % with the maximum in a small study from Hungary with 5.9 % HPV 16.

Oral HPV 16 prevalence in FSWs:

Europe:
CANADAS et al. 2004 (Spain): 2.1 % (N = 188)
MAREK 2014 (Hungary): 5.9 % (small study; N = 34; HPV 16 prevalence data not published/personal communication; control group: 0 % HPV 16)

Outside Europe:
MATSUSHITA et al. 2011 (Japan): 0 % HPV 16, but 1.0 % HPV 18 and 5.1 % HRHPV altogether (note: the relative portion of carcinogenic HPV types differs in East Asia from Europe and North America) (N = 196)
BROWN et al. 2011 (Peru): 0.54 % (N = 184) (note: oral sex 95 % protected by condoms)
CHATTERJEE et al. 2001 (Calcutta, India): 29.0 % HPV 16 and/or 18 (N = 69); however, there are some doubts about the adequacy of the methods of this study, so this study should not be considered as very relevant (too many false-positives or simple contaminations?)

Nevertheless, estimating 2 – 6 % as the relevant oral HPV 16 prevalence in FSWs in Europe, this prevalence is up to seven- to twentyfold compared to women of the general population, where it was found to be 0.3 % in the very large NHANES population from US (D'SOUZA et al. 2014; GILLISON et al. 2012; SONAWANE et al. 2017).

So, as expected, FSWs have indeed a much higher risk of oral/oropharyngeal HPV16 infection compared to other women. In most studies on FSWs it is also not clear how much unprotected oral sex was involved at all. In Peru, where oral sex was performed protected almost every time, oral HPV 16 prevalence was not much higher than in NHANES (0.54 vs. 0.3 %). Even in the Hungarian Study, many FSWs said they use condoms for oral sex. So there is at least some possibility that oral HPV 16 prevalence might be even higher in FSW populations who are used to practice oral sex without protection regularly. However, from

the few available data (except the very problematic "old" study by CHATTERJEE et al.) it is evident that oral HPV 16 prevalence is (much?) smaller in FSWs than their cervical or anal prevalence, and this is also in accordance with oral vs. cervical prevalences in the general population. The same applies to oral HPV 16 prevalence in MSM compared to anal HPV 16. So there are no reasons to assume that oral HPV 16 prevalence in FSWs might be as high or even higher than their cervical HPV 16 prevalence. As indicated by data from people from the NHANES population with 25 and more lifetime oral sex partners (see BROUWER et al. 2019), the oral HPV 16/18 prevalence seems to level out in cases of very high risk exposition; i.e. in highly exposed groups, oral HPV 16/18 prevalence rises disproportionately if the (already high) risk increases further. There is probably some kind of "saturation" and a maximal prevalence level. However, due to the lack of enough epidemiological data for high risk (= highly exposed) persons, and also some heterogeneity in the methods of oral/oropharyngeal sampling and HPV detection, it is so far impossible to quantify this maximal risk level, and it may be different depending on sex, age, smoking or HIV status, since all of them influence natural immunity against oral/oropharyngeal HPV.

Anyway, with regard to vaccination it is important to note that oral prevalence is (much?) lower than the genital prevalence in women of the general population and also in FSWs, and this may explain why the effectiveness of HPV vaccination (mostly Gardasil) in NHANES was shown to be stronger with regard to oral infections (HPV 16/18) (risk reduction: 90 – 100 %) than for cervicovaginal infections (risk reduction: 80 %) (age group: 18 – 24 years; NHANES; BROUWER et al. 2019).

These differences between cervical and oral/oropharyngeal prevalence are also expected for histological reasons. HPV contamination doesn't result inevitably in true HPV infection. HPV needs micro-cracks or microabrasions of the mucosal epithelium to get access to the basal cell layer of the epithelium. Whereas the cervical epithelium is (in part) only one-layered, and the anal epithelium, though thicker, often hurt by micro-cracks or microabrasions (if not from anal sex, then from defecation or cleaning procedures, or some grade of inflammation as a consequence of these micro-traumata or eczemas), the epithelium in the mouth and pharynx is thicker and much more resistant, except for some problematic areas in the crypts of the tonsils (which are therefore much more frequently affected by HPV 16 and HPV-associated cancer than other sites in the mouth and pharynx). In summary, it has to be expected that the oral/oropharyngeal HPV 16 prevalence in the mouth and oropharynx is smaller compared to the cervical or anal site even in heavily exposed individuals like FSWs. Oral contamination with HPV 16 results more rarely in a true infection compared to cervical or anal contamination.

This is an important aspect with regard to vaccination: all available vaccines cover the most relevant HPV types for OOPC in Europe and North America (to at least 95 %), and since the oral/oropharyngeal HPV 16 prevalence in FSWs seems to be (much?) smaller than 10 %, the "too-late-argument", which may apply to a substantial portion of FSWs with regard to cervical and/or anal infection, does therefore not apply so strongly to the prevention of oral infections by the vaccine. And, most important in this context, a detailed analysis of the Costa Rica Vaccine Trial showed that a prevalent infection at one mucosal site (e.g., cervical or anal) at the time of vaccination doesn't impair the effectiveness of the vaccination against new infections at other mucosal sites (e.g. oral) which were uninfected at the time of vaccination (BEACHLER et al. 2016).

The Costa Rica Vaccine Trial (CVT) (HERRERO et al. 2013) proved that the bivalent vaccine protected young women (18 – 26 years at the time of the first dose of the vaccine) against prevalent oral HPV16/18 infection four years later (risk reduction 93.3 % for HPV 16+18), and the ACTG A5298 trial cited in SCHIM VAN DER LOEFF et al. demonstrated the effectiveness of Gardasil 4 against persistent (!) oral infections of the four vaccine types even in older and immunocompromised (HIV-infected) individuals, mostly men (point estimate: 88 % risk reduction of persistent oral infections). Due to small numbers of oral infections, the confidence interval around this point estimate was large; however, in spite of the small numbers of persistent oral infections statistical significance was reached. It is also important that this "oral success" was discovered in the same study which demonstrated the inefficacy (or low efficacy) of the vaccine against persistent anal infections in this heavily pre-exposed population. Thus the study design was able to demonstrate this fundamental difference between the effects of vaccination with regard to the anal versus oral site in this very special population. This is a second proof for the result from the CVT (BEACHLER et al. 2016), that an infection at one mucosal site doesn't impair the effectiveness of the vaccine at other currently uninfected mucosal sites.

Also several papers based on the NHANES population in US demonstrated a high efficacy (about 80 – 100 %) of HPV vaccination (usually Gardasil 4) against prevalent oral infections in men and women, but the age at the time of vaccination is not so clear in this population (HIRTH et al. 2017; SONAWANE et al. 2017; CHATURVEDI et al. 2018; BROUWER et al. 2019). However, available data suggest that most participants got the vaccine "too late", i.e. 18 years or older (mean age for vaccination was 18.5 years in the data from CHATURVEDI et al.), especially if one respects that sexual life in US often starts with oral sex (see GUPTA et al. 2019 for discussion).

And a cross-sectional study from UK (MEHANNA et al. 2018) showed a 91 % risk reduction of oral/oropharyngeal HPV 16 infections in vaccinated girls and young women (N = 243; 12 – 24 years, median: 18.6 years) compared to unvaccinated (0.5 % vs. 5.6 %; p = 0.04). Most or all of the vaccinated girls had received Gardasil (the vaccine applied by the UK NHS for the vaccine program of school girls). All participants of this study got tonsillectomy for non-malignant reasons. Oral samples for HPV testing were collected by oral rinse, tongue base and pharyngeal wall brushes, and by examination of the tonsil tissue following tonsillectomy. This extensive sampling, much more extensive than in any other study concerning oral HPV prevalence, may contribute to the unusually high HPV 16 prevalence of 5.6 % in the unvaccinated girls and young women among the tonsillectomy patients (see below).

This study not only demonstrates the high efficacy of the vaccine to reduce oral/oropharyngeal HPV 16 prevalence, but it also showed signs of herd immunity. All 69 boys in this study were free of oral/oropharyngeal HPV 16, though no boy had gotten the vaccine (HPV 16: unvaccinated boys: 0.0 %; unvaccinated girls: 5,6 %). 78 % of the girls were vaccinated, which may explain the protection of the boys and young men.

The high oral prevalence of HPV16 in unvaccinated girls and young women from the general population who got tonsillectomiced in the MEHANNA study contrasts to all known epidemiological data for women from the general population (e.g., the very large NHANES data set). However, besides the most extensive oral/oropharyngeal sampling ever done,

young people with hypertrophic or chronically infected tonsils may be much more prone to oropharyngeal HPV infections (and their persistence) than those with healthy tonsils, because in these cases HPV particles have easy access to the basal layers of the epithelium ("entry port"). The high prevalence may thus be a consequence of longer lasting tonsil pathology which may have made the tonsils more susceptible to HPV infection in the case of HPV contamination. In fact, it was already shown that people who were tonsillectomiced in former times have a reduced risk of oral/oropharyngeal HPV infection (BEACHLER et al. 2015). So it is not unexpected that people with chronically infected and/or hypertrophic tonsils may have a higher risk for HPV infection in the oropharyngeal area, or persistence of HPV at that site. Chronic inflammation may impair clearance and promote persistence, what may also explain the high prevalence in tonsillectomy patients.

Nevertheless, since all participants of that study suffered from tonsillar disease which gave reason for tonsillectomy, these considerations don't affect the quality of evidence as far as the effectiveness of the vaccine is concerned; they only explain while people with chronic tonsillitis or tonsillar hypertrophy may be another high risk group for oropharyngeal HPV (16). If one acknowledges this aspect, one can consider the MEHANNA study as another "risk group study" on oral vaccine efficacy of Gardasil (4) (like the A5298 trial, which was also a risk group study, but for very different reasons).

Nevertheless, the ACTG A5298 trial is the most important trial in the context of oral infections in risk groups so far because it is the only trial which looked after ***persistent*** oral infections (only they matter with regard to cancer risk) and since it was carried out in a heavily exposed and pre-exposed population. Because HIV infection increases the risks of incident and prevalent oral HPV infections, the A5298 study population may tentatively reflect the oral risk level of FSWs. In fact, some studies on HIV infected populations (mostly MSM) demonstrated oral HPV 16 prevalences close to the 5.9 % in the small Hungarian FSW study or the 6.5 % HPV16/18 in NHANES men and women who had 25 or more oral sex partners in their lifetime (GUPTA et al. 2019). So there are good reasons to assume a close proximity of the A5298 trial to the oral HPV risk situation of FSWs who practice unprotected oral sex with their clients (and possibly colleagues), and these favorable A5298 data (Gardasil) are supplemented by the 93.3 % efficacy of Cervarix against prevalent oral HPV 16/18 infections four years after the first vaccine dose in women aged 18-26, i.e. in an age group when many FSWs start their sex work (in accordance with the own experiences of the authors in the first chapter of their article).

So there is already some evidence in favor of HPV vaccination for FSWs who practice unprotected oral sex with their clients (and colleagues). The efficacy of the vaccine against HPV-associated OOPC in (former) FSWs will never be demonstrated in trials due to the methodological limitations mentioned above. In the absence of cytological precursors like CIN or AIN in the oropharynx and due to the long latency until OOPC develops, there is a general consensus that *the prevention of persistent infections is an acceptable endpoint in HPV vaccination studies* with regard to the oral effectiveness of the vaccine ("The Primary Endpoints for Prophylactic HPV Vaccine Trial Committee", IARC/U.S. National Cancer Institute) (LOWY et al. 2015). The A 5298 (WILKIN et al. 2018) trial is so far the only trial in accordance with this recommendation.

Taken this into account, we already have some good evidence to offer HPV vaccination to FSWs who like to practice unprotected oral sex, and it is not probable that we will get better evidence in the near future. Of course more studies concerning the oral HPV 16 epidemiology in FSWs are urgently needed. For example, it would be interesting to see the correlation between oral HPV 16 prevalence and the frequency of unprotected oral sex in the last 1 or 2 years, at best distinguishing between fellatio and cunnilingus (on colleagues). Such a study would be feasible with one-time-examination (mouth wash/gurgle sample and questionnaire) and thus not methodologically impossible. However, since unprotected fellatio is forbidden in Germany, such studies cannot be performed in Germany since those FSWs who continue to offer unprotected oral sex to their clients in spite of the law would not admit this in the questionnaire due to the legal restrictions, making any study of this kind useless or at least prone to extreme bias. However, in spite of the small number of available studies, we already have better *indirect* evidence for the protective effect of HPV vaccination of FSWs against (persistent) oral infections than against cervical or anal infections in potentially/probably heavily pre-exposed FSWs.

Oral HPV risks for clients

There is a second important aspect in the context of oral sex. Many clients like to practice unprotected cunnilingus on FSWs (dental dams are used extremely rare, about 1 %). Some FSWs don't allow cunnilingus; they may fear micro-traumata on the genital mucosa which may facilitate STI acquisition, or they tend to suffer from candidiasis after unprotected cunnilingus. However, many FSWs like cunnilingus, either for their own pleasure or to relax and to be able to stay a while "passive" during "paid time". I estimate that about 35 – 50 % of all paid contacts with FSWs in Germany involve some cunnilingus. These estimates are based on two independent methods in a clients' forum in Germany: (i) a questionnaire (35 – 45 % cunnilingus per contact; n = 578 participants) and (ii) the detailed analysis of forum reports from clients about single contacts with a FSW (so called "fuck-reports") (> 55 % cunnilingus per contact; n = 184 reports). The latter may be biased towards longer or more complex meetings with FSWs (which are more "worth" to be reported in the forum) what may explain the difference between the results of the questionnaire and the analysis of the reports. However, only 15 % of the participants of the questionnaire said that they never lick on FSWs. Dental dams were used by about 1 % of the clients (n = 578).

Due to the high genital prevalence of HRHPV in unvaccinated FSWs (and the usually high concordance between cervical und vulvar infections), these clients have a high risk of oral HRHPV contamination and infection. As mentioned above, the viral load on female genital mucosa is assumed to be higher than on the surface of the penis; moreover, many FSWs are heavy smokers and smoking is known to increase viral shedding at any infected mucosal site. Men also miss a possible naturally generated immunity as a result of genital contamination or infection which may generate some humoral or antibody-based protection also at the oral site in women (see D'SOUZA et al. 2016). Among all HPV-associated cancers in men, oropharyngeal cancer is the most prevalent (RKI 2018a), much more prevalent than anal or penile cancer.

And it is also well established that husbands of women who had higher-grade CIN or cervical cancer in their life history, have a higher risk of OOPC (e.g. CHANCELLOR et al 2017; HEMMINKI K et al. 2000).

Thus, men who like to practice unprotected cunnilingus on unvaccinated FSWs belong to the top risk groups for prevalent and persistent oral/oropharyngeal HPV 16/18 infections, and, as a consequence, HPV-associated OOPC. Depending on the frequency of this practice, they may even surpass HIV-infected MSM with regard to their risk of HPV-associated OOPC.

From a public health view it might be desirable to recommend HPV vaccination to FSWs who like to be licked by their clients, as well as for their own protection (clients with HPV in saliva might infect the genital mucosa of FSWs, though this way seems to be less effective than the opposite direction from vulvar mucosa to mouth and pharynx, due to higher viral load there compared to saliva) as for the protection of their clients.

Since (i) recommendation of HPV vaccination to FSWs (or at least subgroups of FSWs) is not established so far, and since (ii) the probability, that any given FSW may have received the vaccine in the past is very small (I agree fully to what SCHIM VAN DER LOEFF wrote in their paper about that subject, and this is also corroborated by own experiences), I go so far to recommend HPV vaccination to those clients who like to practice unprotected cunnilingus on FSWs. The immunogenicity of the HPV vaccine is already proved for adult men, even for Gardasil which results in lower antibody titres than Cervarix (for Gardasil 4: PINTO et al. 2016); the same applies to the A5298 trial in an age group that was on average older (median: 47 years) than that of the PINTO study. However, in the male PINTO cohort (Gardasil 4), by months 18 and 30, oral antibodies were only detectable in some participants (HPV-16, 39.8% and 29.6%; HPV-18, 10.7% and 4.6% of individuals) (PARKER et al. 2019). This doesn't mean that oral protection vanished during this time. If protection against prevalent oral infection vanishes so quickly, the epidemiological data which support a high efficacy of Gardasil alone (NHANES men) or mixed use of Gardasil and Cervarix (but mostly dominated by Gardasil) like NHANES (women) or the MEHANNA tonsillectomy study (Gardasil 4) would be impossible (the UK National Health Service program for HPV vaccination of girls used Gardasil). In the absence of detectable oral antibodies, oral contamination might booster antibody production before a productive, stable infection is established in vaccinated individuals.

Before the results of the A5298 trial were available, it seemed obvious to recommend Cervarix to clients of FSWs if the primary purpose of vaccination was oral sex. It is well-known that Cervarix generates higher antibody titres (measured as geometric median) than Gardasil, and it was also shown that the antibody titre in the oral fluid is 2 – 3 orders of magnitude smaller than in blood serum (PINTO et al. 2016). Though antibodies against HPV 16 were present in the oral fluid of 96 % of adult men after Gardasil(4) vaccination (PINTO et al. 2016), the titres were so low that one might question whether they are fully protective (the PINTO study didn't look for oral infections; it was about antibody titres in serum and oral fluid).

With regard to Cervarix, we already know about its protective effect against prevalent oral infections in young adults from the CVT since the end of 2012 (HERRERO et al. 2013).

Before A5298, NHANES-based studies and MEHANNA et al., evidence for efficacy against oral infections was better for Cervarix than for Gardasil, and the low antibody titres following Gardasil vaccination caused some doubts about its oral/oropharyngeal efficacy.

This gave reason to recommend Cervarix (and safe some money) to men who like to lick on FSWs (as main reason for vaccination), because higher antibody titres in the oral fluid can be expected after Cervarix vaccination. It was found in the Gardasil trial with adult men (PINTO et al. 2016, PARKER et al. 2019), that, on an individual base, the titres of antibodies in oral fluid and blood serum are closely correlated to one another (as expected).

However, with the results of the A5298 trial and also some NHANES data (in US, nearly all vaccinated people got Gardasil, and as long as Cervarix was available there, it was not approved for men, so 100 % of vaccinated men should have gotten Gardasil), Gardasil may also be recommended to men who like to practice cunnilingus on FSWs. Because of the limited protection of condoms against HPV, the protective effect of Gardasil against genital warts (if not currently infected) may also be interesting for clients. There was a report from a FSW in a forum who was interested in anogenital warts and counted the clients with such lesions. She reported anogenital warts on every seventh client; however, no one knows whether her diagnosis was correct or whether she misclassified some other lesions as anogenital warts. Nevertheless, this report shows that anogenital warts are in fact a problem for clients of FSWs.

Meanwhile, the role of the HPV vaccine for the prevention of HPV-associated oral and oropharyngeal cancer is regarded as so important and conclusive that there are recommendations in the US that also dentists should promote and offer vaccination (American Dental Association 2012 and 2018; National HPV Vaccination Roundtable) (KEPKA D et al. 2019).

Herd immunity

As mentioned in the article from SCHIM VAN DER LOEFF et al, there are also aspects of herd immunity. But not only for clients and other women (partners of the clients) and the general population, but also for FSWs themselves. The more FSWs are vaccinated, the smaller the risk for the remaining unvaccinated FSWs or young beginners who didn't had already the chance for vaccination, due to lack of consultation/recommendation or money.

It is well established that herd immunity works well with regard to HPV vaccination. Though the best example for that is the nearly complete eradication of genital warts in the young generation in Australia (though only girls had been vaccinated, boys/young men had an enormous profit from that), there are also examples from other countries with comparatively high vaccination rates in schoolgirls (e.g. Sweden, UK; for systematic review and meta-analysis see DROLET et al. 2019).

In a sexual network, those who didn't get the vaccine profit from vaccination of others. This doesn't work only in very tight sexual networks, but to a lower extent and with some temporal delay even in very loose and weak networks. So, for example, a reduction in the

prevalence of genital warts in young homosexual men in Australia was found as a consequence of the vaccination of most of the schoolgirls (FAIRLEY et al. 2012).

FSWs from the same sex work setting (e.g. brothel, club), but even in the same local (geographical) area are interconnected with one another in a more or less tight sexual network not only via direct interaction (lesbian games, threesomes) inside their sex work setting, but also (and to a larger extent) via their clients, who often contact several FSWs in the same setting or local area, if not at the same day, then sometime in the past or future. This results in a tight sexual network within the same setting and a less tight network in the local area between FSWs and clients, with private partners of the clients and of the FSWs in the periphery of that network. Infected private male partners of FSWs may serve as a reservoir for HPV reinfection or HPV reloading of FSWs (ping-pong effect), especially if they don't use condoms, and thus impair clearance of prevalent HPV infections (which then may become persistent) or regression of CIN lesions. The lower the HPV burden in this local (setting-specific or regional) sexual network, the lower the future HPV risks for those FSWs who didn't get vaccination.

Conclusions

In summary, I agree with SCHIM VAN DER LOEFF's discussion that the recommendation for (or against) HPV vaccination must be balanced for each individual FSW, and vaccination should only be recommended when this balance favors vaccination. Unprotected oral sex, active (on clients and colleagues) and/or passive (cunnilingus by clients) should be considered in favor of vaccination. In contrast to cervical cancer, there is currently no secondary prevention/early detection program available against HPV-associated OOPC, leaving vaccination as the only way of prevention if one doesn't accept to practice any form of oral sex consequently with barrier protection (see GUPTA et al. 2019) (though even in the case of consequently protected oral sex some residual risks remain, for example (i) licking at the scrotum which may also be infected by HPV – as proven by genital warts on the scrotum; (ii) self-inoculation from the genital/vulvar to the oral site in case that the condom is not changed when fellatio is practiced following vaginal intercourse, e.g. to improve or regain erection; (iii) erroneously turning around the dental dam or other removable barriers during cunnilingus so that the contaminated side of the barrier gets in close contact to the tongue).

The bandwidth how much an individual FSW may profit from vaccination, is large: On one side there are very young, maybe 18 yrs. old beginners in sex work with no or little sexual experience before, as SCHIM VAN DER LOEFF et al. already discussed in their paper (they really exist, e.g. from rural areas and traditional families in Romania or Bulgaria). Because of the high HPV risks of sex work (and the limited protective effect of condoms, estimated to be only 50 – 70 %), those FSWs will probably profit much more from HPV vaccination than an early (< 15 yrs.) vaccinated girl from the general population who won't engage in sex work later in life. Some studies found up to 10-fold risks of cervical high-risk-HPV prevalence in FSWs compared to age-matched controls (e.g. TOUZE et al. 2001), and a (not peer-reviewed) review about the relative risks of cervical pathologies in FSWs found a four- to fivefold risk of higher-grade dysplasia like CIN2+ or HSIL in FSWs compared to women

of the general population (own results in a forum-based paper; includes 8 studies with 6965 FSWs and even more controls).

Thus, a young beginner in sex work with no or little sexual experience in the past is expected to profit much more from vaccination than girls from the general population, though such cases may be rare. In these cases, vaccination of the beginner may prevent much more HPV-associated disease burden than the "early" (< 15 yrs.) vaccination of a young girl of the general population with average sexual behavior/risks in later life can do.

However, in countries where SW have to be counselled before starting sex work (like Germany), it is (at least theoretically) feasible to recommend HPV vaccination (and to give the first dose of the vaccine) before sex work is started. Since antibody titres rise quickly after that dose, protection against HPV will start during the second week after injection.

On the other extreme boundary of that bandwidth are experienced FSWs in their late 30ths, 40ths or 50ths with a long history of sex work. If they participated in cervical/genital cancer prevention/early detection programs on a regular base and never had any HPV-associated pathology, they have obviously no problems to avoid or clear incident genital HPV infections and have an effective natural immunity against HPV. And maybe they offer only protected oral sex and/or want to stop sex work not so long time in the future. Their profit from vaccination is probably very small or nearly zero and doesn't outweigh the costs and inconveniences and possible (local/systemic) side effects of vaccination, whoever pays for it, even if is for free. Also the HPV risks for their clients are expected to be much smaller (compared to young FSWs), though they still exist. Thus vaccination of such FSWs would have only smaller effects on client protection and herd immunity.

These two examples show the extreme boundaries of the large bandwidth. Most FSWs will have to be categorized somewhere between these extremes; as SCHIM VAN DER LOEFF et al. wrote: *"not all SW are the same".*

There are many criteria which may have to be taken into account to estimate whether an individual FSW will profit more or less from vaccination, and whether vaccination should be recommended to this individual FSW, or whether the expected profit is probably too small if one compares it with costs, inconveniences, side effects and risks? Such criteria may be:

- calendar age ("very young")
- sexual experience in the past (lifetime and especially during the last 1 – 2 years, the usual clearing time of HPV infections)
- time in sex work/history of sex work/number of "vaginal" clients in the past
- plans for the future: how long does she want to continue sex work?
- results of former cervical cancer screenings, history of HPV infections or HPV-associated pathologies (also as a proxy for natural immunocompetence against HPV)
- offered sexual services and non-genital (for example oral) HPV risks?
  (e.g., unprotected oral sex;
  unprotected fellatio on clients,
  unprotected lesbian action with other FSWs;
  unprotected cunnilingus from clients)

- smoking (reduces the chance of spontaneous clearance of HPV infections at any mucosal site, enhances viral shedding and infectiousness)
- combination of smoking and unprotected oral sex

if available:

- current cervical HPV status (if HPV 16 is present without pathology, it is an open question whether it is recommendable to delay vaccination until this infection cleared. This rises also the question whether cervical HPV testing before vaccination should be recommended to active/heavily pre-exposed FSWs?) (see below)
- current HPV-associated pathology (according to most trials, HPV vaccination reduces the risk of recurrence after treatment/removal of CIN2+, especially if administered as adjuvant to surgical treatment)

Based on these (and maybe some additional) criteria, it might be theoretically possible to develop a score to grade the individual strength of recommendation for or against HPV vaccination for an individual FSW. However, there are not enough epidemiological data to weigh out each criterion against the other ones, and to validate and calibrate the score. Furthermore, there are secondary criteria like access or participation in cervical cancer screening (those who don't participate may profit more from vaccination because they don't have the chance of early detection) or psychological aspects. A FSW may feel better during work when she knows that she got the vaccine and is protected against new infections, including genital warts which are not life-threatening, but very unpleasant for FSWs. She did the best she could do against HPV-associated diseases (besides cervical cancer screening), and this may relax psychologically, independent of how much she can profit from vaccination according to objective calculations. Thus vaccination may contribute to psychological health of FSWs who worry about infection risks, and psychological health is an important and often debated matter for FSWs.

So, in summary, I agree with SCHIM VAN DER LOEFF's paper that the primary question is not whether to recommend HPV vaccination either to all FSWs or to none of them, but to recommend HPV vaccination to those FSWs (and beginners of SW) who will profit most from it, or who want it on their own (maybe for psychological relief because they want to do the best against HPV what is possible and to feel protected, as a contribution to their psychic health).

And of course the same applies to MSW or transgender SW (though some criteria must be adapted), but also to some male clients of FSWs as already described above.

Costs of vaccination

A main obstacle are the high costs of vaccination; those FSWs who might profit the most (like the young beginners) might have the strongest (financial) limitations to get the vaccine because they have no money – otherwise most of them wouldn't start sex work at all. It is well established meanwhile that most FSWs would accept the vaccine and wish to get it, if it is for free, are at least much cheaper than it actually is (e.g. Peru: BROWN et al. 2012; BROWN et al. 2013; Netherlands: MARRA et al. 2017; China: HONG et al. 2013;

Cambodia: WADHERA et al. 2015; Hungary: MAREK et al. 2014; more indirectly: Antwerp: PELEMAN 2015).

So, in real life, beyond science and the different grades of scientific evidence, the balance is not so much between the "pros and cons" based on scientific evidence (in the worst case, an individual FSW may profit only very little, but her clients and their private partners as well as her own private partners can profit) but much more between the "pros" and the high costs. The "pros" must outweigh the high costs, and this is difficult to estimate or calculate on an individual base, especially in a population which is prone to financial problems and different degrees of pre-exposition to HPV.

But as already mentioned above, also secondary and subjective criteria have to be taken into account. From the public health view, offering vaccination for FSWs for free would be optimal in order to reach many FSWs (including those who would profit at most like the young beginners) and to generate some impact on herd immunity in their sexual network and the general population.

One idea based on some data from the ARBYN Cochrane review (ARBYN et al. 2018) is that one might reduce the number of vaccine doses in financially deprived young FSWs (< 25 years) to one or two doses, but the evidence for this reduction is much better for Cervarix than for Gardasil (in general, if all three doses are expected to be taken, one should favor Gardasil 9 for FSWs because of several advantages). But it is not so clear from these prospective trials whether the protective effect of 1 or 2 doses Cervarix lasts for as many years as that of three doses (a matter which is still open to debate in general), but many financially deprived young women practice sex work only for a few years until their financial situation improved, so even a limited protective effect (as far as the duration of the protection is concerned) of a reduced, suboptimal vaccination schedule might be (nearly) as protective for them as three doses.

However, since median antibody titres are higher following Cervarix vaccination, favorable results from Cervarix trials (like the efficacy of 1 or 2 doses in young women < 25 years) cannot be applied directly to Gardasil vaccination. In fact, the case-control study from SILVERBERG et al. warns that 1 or 2 doses of Gardasil offer much less protection than 3 doses even in teenagers (aged 14 – 17 years) if one looks at the prevalence/incidence of CIN2+ or 3+ about 10 years after the first dose (the mean age of the women was 26.3 years at the time of study examination). In the Healthplan Setting in the San Francisco Bay area of the SILVERBERG study, only Gardasil (4) was applied; the study stopped too early to include participants who got Gardasil 9. Thus it is very evident now that a dose reduction (1 or 2 doses) of Gardasil cannot be recommended even in teenagers (beyond 14 years) and very young adults. This conclusion is also corroborated by several Gardasil studies mentioned in the discussion part of the SILVERBERG paper.

Nevertheless, because of many advantages Gardasil 9 should be preferred for FSWs, but then there is no discussion about the number of vaccine doses needed, independent of age. Thus the high costs are the most important hindrance for vaccination.

But there are several possibilities to reduce the costs without dose reduction. Foreign FSWs might get the vaccine for lower costs in their home country; however this would delay vaccination until the next visit at home and may thus reduce its effectiveness due to infection risks in the meantime. It would be optimal for them to get the vaccine (at least the first dose) before they travel to western countries for sex work, but they probably don't know about the advantages of the vaccination and also won't have the money for that in their home country, even if is cheaper there than in western countries.

Some Health Insurances in Germany pay for HPV vaccination on a voluntary base until the age of 26 (so-called "Satzungsleistung"). However, an official recommendation for FSWs and other adult persons with high HPV risks from Public Health Authorities (in Germany: Robert-Koch-Institut; STIKO) would considerably increase the chance that Health Insurances pay for vaccination. Such a recommendation must not contrast to our views (SCHIM VAN DER LOEFF's paper and this comment), that the decision pro or contra vaccination should be made on an individual balance and that there is too little evidence in favor of a "general recommendation" which fits to all individual FSWs. The official recommendation can point to the need for such an individual balance.

Furthermore, cost effectiveness is an important aspect for Public Health authorities. The calculations for an age-mixed FSW cohort, based on the 7 years end-result of VIVANE and adapted to the cervical HPV16/18 prevalence in FSWs, hints in favor of cost effectiveness (see below). However, if the authorities still have doubts or want to improve cost effectiveness, they might reduce positive recommendations (based on individual balance) to those FSWs (or adult women at high risks in general) with a negative HPV16-DNA result at the cervix before the first vaccine dose, and/or certain (younger) age groups of FSWs and other highly exposed risk groups. Though this is suboptimal since such recommendations would exclude some FSWs/persons who might profit from vaccination too (e.g. FSWs who are HPV-16-DNA positive at the cervix, but practice a lot of unprotected oral sex), but any recommendation in favor of HPV vaccination of FSWs or subgroups of FSWs is better than no recommendation at all with regard to the question whether health insurances may pay the vaccination. With an official recommendation in the background, it would be much easier for FSWs to get the vaccination from their health insurance, provided they are member of a health insurance at all (many foreign FSWs don't have any health insurance or maybe only a cheap travel health insurance which pays in case of acute illness, but not for vaccination).

In case the FSWs have to pay vaccination by their own, they should keep the bills and fiscal officers should accept these costs as professional outlay if FSWs make a tax return declaration. The professional reason for that vaccination can be compared (from a fiscal office point of view) to Hepatitis B vaccination for medical professions (which applies to FSWs too).

Another important open question is whether it is wise to recommend a cervical HPV test (at least for HPV 16) in FSWs or sexually experienced/pre-exposed women who want to start sex work in order to respect the results of this test in the balance of the "pros and cons". Of course the test must be able to detect HPV 16 specifically (and not only "HPV" or "HRHPV" in general). Meanwhile, there are also self-tests on the market, and vaginal smears seem to be at least as effective (and probably more effective) than cervical smears to detect infections.

It is not generally recommended to do such a test before vaccination or to make vaccination dependent on it, but the situation may be very different in a (heavily) pre-exposed population like active FSWs, compared to the vaccination routine for children and adolescents of the general population. The combined data from several studies mentioned in the ARBYN review clearly show that a current infection with HPV 16/18 at the time of vaccination reduces the protective effect of the vaccine against HPV16/18-associated CIN2+ within the follow-up period of (in most studies) 3 to < 4 years to nearly zero, whereas seropositivity alone (i.e. in the absence of a current infection) results only in a small reduction of the vaccine efficacy with regard to the same endpoint. In other words: clearance of an infection which was present before vaccination (but no longer during vaccination) results in an effectiveness of the vaccine close to that in naïve (or presumed to be naïve, "pseudo-naïve") women. This rises the question whether it is better to delay vaccination until the current HPV 16 infection is cleared in women who are HPV 16 –positive (cervical) at the time when vaccination is intended. If one follows this concept, a cervical HPV(16) test prior to the first dose should be recommended to heavily pre-exposed women. A negative test would then mean a big "pro" in favor of vaccination. A positive test would result in the need to rebalance the decision on vaccination, especially the time of vaccination. There still may be reasons not to delay the vaccination until cervical HPV 16 cleared, e.g. protection with regard to unprotected oral sex as mentioned above, or protection of clients who perform unprotected cunnilingus (since they have a high risk when it is already proven that the genital area of the FSW is infected by HPV 16). It would be wise to recommend to these FSWs that they don't allow unprotected cunnilingus to their clients until the infection cleared if they don't take the vaccine:

Firstly for the protection of their clients, but also for the currently infected FSW herself: frequent cunnilingus might delay HPV clearance due to micro-traumata or low-grade inflammation (caused by some components/antigens from the saliva or secondary to micro-traumata).

I don't think that cervical HPV (16) testing before vaccination should be recommended in every case when HPV vaccination of active FSWs or beginners is considered. But it may help to improve the accuracy of the balance in individual cases when the balance is less clear. But there is one important exception: if a HPV-type from the vaccine is present at the cervix and associated with a pathology which has to be treated locally/surgically, vaccination is recommended in order to reduce the risk of recurrence (as mentioned also in SCHIM VAN DER LOEFF et al.).

Missing studies from the FSW population

I don't expect that we get better evidence (pro or contra) in the next years. The highly mobile, internationally working and often anonymous FSW population is not available for long lasting RCTs. Such RCTs would have to last at least 7 years or (better) longer. The problem with most of the published prospective trials with young or middle-aged adult women was the short duration of 3 – 4 years (see ARBYN et al., where all of these studies are summarized in the several tables). It is known that it takes about 4 years (or more) from a new (incident) infection (which later became persistent) to develop into CIN2+ (e.g. VINK et al. 2011: mean 3.75 years) or CIN3 (e.g. RKI 2008b: 3 – 6 years, i.e. mean ~ 4.5 years).

It is well-known that vaccination doesn't affect the natural history and fate of an infection which is already present at the time of vaccination. So what should one expect 3 or 4 years after the first vaccine dose in potentially/probably/heavily pre-exposed women, if CIN2+ or CIN3 is the endpoint? In fact: nothing or something very little and insignificant.

When a trial is cut after 3 or 4 years, one may be able to see a reduction of incident, prevalent or persistent infections of HPV types from the vaccine (and some cross protection) in the vaccine group, maybe also reductions of CIN1 (however, one should respect that CIN1 is not so tightly correlated with HRV 16/18 or HRHPV in general as CIN2+), but one cannot expect a significant reduction in CIN2+ or CIN3 because all or most CIN2+ which occur in this time window of the first 3 – 4 years after the first vaccine dose develop due to infections which were already present at the time of vaccination. Even if the trial involved a cervical HPV test at start, it could have been false-negative in those cases who develop CIN2+ or CIN3 during the first ~ 3 years after the first dose. The accuracy of these tests is not 100 %, or the prevalent infection was in a latent stage at the time of testing.

Thus a reduction of CIN2+/CIN3 cannot be expected before year 4 or 5 in potentially/probably (heavily) pre-exposed women. In fact, the final results of the VIVIANE trial (WHEELER et al. 2016) (with an average age of 37 at the time of vaccination and a pre-exposition with regard to HPV16/18 which was heavier than what is expected in the general population) found two cases of CIN3+ in the vaccine group and six cases in the control group in the years 5 – 7, while there was no profit from the vaccine with regard to CIN2+ and CIN3+ in the years 1 – 4. This means a risk reduction of 67 % for CIN 3+ (irrespective of HPV type) in the vaccine group in the years 5 – 7, close to that what can be expected from a vaccine which is only bivalent (70 % or 70 – 80 %, but not more for the distant endpoints).

But the need for local treatment at the cervix was reduced by 62 % in the years 5 – 7, compared to the control group (10 versus 26 cases), and this difference was significant. Both endpoints (CIN 3, need for local treatment) are of high practical relevance for FSWs. Maybe a prevalent or persistent infection or CIN 1 doesn't (or shouldn't) worry them a lot (at least in "younger" years), but a CIN 3 or the need for treatment at the cervix is an important undesirable event and means some or a lot of inconveniences, costs and also risks.

Contrary to local treatment needs (- 62 %; sign.), due to the small numbers of CIN 3+ cases in this age group, including the control group (the VIVIANE women had reached a mean age of 44 years when the trial stopped), the difference in CIN3 (2 : 6) is not significant. The study was underpowered to find a significant difference for CIN 3 in this "old" age group (where the incidence of CIN2+ or 3+ is lower than in younger age groups even in the absence of vaccination), or the trial stopped too early to make the difference significant. However, there were significant reductions of CIN1+ (irrespective of HPV type) in months 48 – 84 (-48.1 %) in the total vaccinated cohort (i.e. irrespective of HPV pre-exposition), of CIN 1+ (HPV16/18-associated) at month 84 in the total vaccinated cohort for efficacy (i.e. only pre-exposition to either HPV 16 or 18 was allowed) (-75.5 %) and non-significant reductions of CIN 1+(16/18) (-75.5 %) and CIN 2+(16/18) (-80.4 %) in the same cohort at month 48 and a nearly significant reduction (missing significance just a little) of 78.2 % for CIN2+(16/18). Taken all of these results into account, it is highly improbable that the reduction of CIN 3 (-67 %) in years 5 – 7, though formally insignificant, is the result of a random.

Thus the VIVIANE trial made it clear that vaccine trials in adult, (possibly/probably/heavily) pre-exposed women should last much longer than four years if one wants to look at endpoints of clinical relevance like CIN2+/CIN3+ or the need for treatment at the cervix. But those are the endpoints which are really interesting and relevant for the FSWs themselves. It can be modelled from these final results of the VIVIANE trial, that less than 25 FSWs of an age-mixed cohort of FSWs (but younger than VIVIANE on average) would have to be vaccinated to prevent *one case of need for treatment at the cervix* in the years 1 – 7 after vaccination, and thus much less than 25 to prevent one case of need for treatment lifelong after vaccination (own results in a forum-based paper). The model is based on table 4 in WHEELER et al; it is calculated in table 4 that 143 local cervical treatments can be prevented by Cervarix per 100.000 women-years of the study population (mean age at first vaccine dose: 37 years) in the first seven years after the first vaccine dose, i.e. 143 per (100.000 : 7) = 14.283 women within seven years, i.e. 1 per 100 women of the study population within the first seven years after the first dose.

The model calculation for an age-mixed cohort of FSWs is based (i) on 15 % cervical HPV16 or 18 prevalence at the time of vaccination (according to SOOHOO et al. for FSWs from Europe, but also in full agreement with own data from Amsterdam from SCHIM VAN DER LOEFF's group [MARRA et al. 2018]), contrary to "only" 4 % in the total vaccinated cohort from VIVIANE, and (ii) a 4.5-fold risk for treatment needs at the cervix in unvaccinated FSWs compared to unvaccinated control women (based on 4- to 5-fold risk for CIN2+ or HSIL in the meta-analysis from 8 studies with 6965 FSWs and even more controls mentioned above).

In an analogous way one may calculate that (much?) less than 35 FSWs of an age-mixed cohort (but on average significantly younger than VIVIANE) have to be vaccinated to prevent one case of CIN3/CIN3+ in year 5 and beyond (lifelong). How much "less than 35" will depend on the age structure of the cohort (the younger, the less). But this model is less robust because it is based on small numbers (2 : 6 cases of CIN3 in years 5 – 7 in VIVIANE), whereas the database for the calculation of the prevented treatment needs is much more robust and includes statistical significant components (the reduction of treatment needs in years 5 – 7 was found to be significant).

Because RCTs (especially of the recommended duration > 7 years) are not possible in the FSW population, one might consider case-control studies with one-time examination (maybe even anonymous/pseudonymous) to compare the HPV infection or PAP/CIN status of vaccinated FSWs to those who are unvaccinated. This might be interesting, but has also a lot of limitations and may result in "wrong" conclusions with regard to the long-term effectiveness and advantages of the vaccination. First, HPV-DNA (e.g., 16/18) prevalence is not a good indicator since it may even represent a fresh contamination from a client which may not result in a true (stable) infection. Persistent infection (6 or 12 months) is a much better endpoint with higher clinical relevance and avoiding the contamination bias; however it is not available following one-time examination. The next endpoint (after prevalent HPV infection) which is available in one-time examination is PAP grading/CIN.

Second, as the SCHIM VAN DER LOEFF group found in a former paper (MARRA et al. 2017), one cannot rely on the anamnestic history of the FSWs; most of who pretended to have gotten HPV vaccination were unvaccinated and probably confounded HBV and HPV

vaccination. Therefore the HPV vaccination status would have to be verified by serological testing if one needs accurate information for a case-control trial.

Third, if the FSWs have problems to recall correctly whether they got the HPV vaccine, it would be even more difficult for them to remember the exact timing of vaccination. But this is very crucial: As mentioned above, a reduction of CIN 2+ in probably/heavily pre-exposed adult women can only be expected after about 4 years after the first vaccine dose. CIN 2+ which are discovered within the first ~ 3 – 4 years after the first dose are probably due to earlier infections which were already present at the time of the first dose. (In a case-control study, one has no information about HPV status at the time of vaccination). To analyze the long-term efficacy, one should exclude all FSWs who got the vaccine less than 4 years ago, or analyze and present the results (e.g. < 3 years, 3 – 4 years; 4 years and beyond; time since first dose) separately.

Since the answers of the FSWs about the time of their vaccination cannot be verified in most cases (except there are bills or so), this is a fundamental obstacle for such a study. If one doesn't respect the ~ 4 years cut-off in respect to the time since vaccination, such a study may result in the conclusion that HPV vaccination of FSWs is ineffective (as far as cervical CIN2+ status or need for treatment are concerned). And with regard to CIN 2+, one should look for the underlying HPV type and present the results for CIN2+ associated with HPV types from the vaccine separately. Otherwise effects of the vaccine may be overlooked or too much diluted if only "all CIN2+", irrespective of HPV type, are presented. CIN2+ with HPV from the vaccine, especially HPV 16/18, have a higher risk of progression than any CIN2+, so the distinction between CIN2+ (16/18) and CIN2+ (irrespective of HPV type) is not only of academic interest or a trick to improve the statistics of vaccine efficacy in trials funded by the vaccine industry, but it is an important matter of clinical and prognostic relevance and thus it is justified to do so. At best, results for "all CIN2+" (irrespective of HPV type) and CIN2+ (16/18) should be presented both.

Even if the vaccine is highly effective in pre-exposed women, no significant reduction in CIN2+ could be expected during the first 3 – 4 years, so one has to look what happens beyond 4 years, and most RCTs with post-adolescent women failed to do so. Anyway, though the study concept described above (one-time examination, PAP pathology or CIN status, verification of HPV vaccination status by serological tests, documentation of the exact time of vaccination) could work <u>in theory</u> even with FSWs, with CIN2+ or (better) CIN3+ as endpoints and the need to differentiate between "fresh" (1- <4 years) and "old" (4 years and more) vaccination, one would need very high numbers of study participants to avoid underpowering, thus even this kind of one-time examination study is practically impossible.

In summary, I don't expect better evidence with regard to the subject of HPV vaccination of FSWs in the next years, at least as far as trials within the FSW population are concerned. So one will have to keep on relying on indirect evidence in the next years and probably in the next decades.

Contra arguments from SCHIM VAN DER LOEFF et al.

There are some aspects one may consider in the context of the five contra arguments mentioned in the paper.

First, the A5298 trial (WILKIN et al. 2018) is indeed disappointing with regard to persistent anal infections. There was only a non-significant risk reduction of about one quarter. However, this was a small study and the small effect (one quarter) might have been become significant in a larger study population. So it is still open whether the effect of the vaccine with regard to persistent anal infections in a heavily pre-exposed population is truly zero/completely negligible or whether it is small, but still of interest for populations with high anal risks (~ 25 % risk reduction may be better than nothing for people at high risk).

Moreover, it is unclear whether these (disappointing) "anal" results would apply to cervical infections in FSWs too. There is of course a strong epidemiological correlation between cervical and anal infections in women in general and especially in FSWs (e.g., MARRA et al. 2018).

Because only about 16 % of FSWs practice anal sex with clients (due to a recent worldwide meta-analysis; OWEN et al. 2019), which also applies to our area (own data), most anal infections in FSWs may be due to smear infections from the genital area, i.e. autoinoculation. The ACTG A5298 population was dominated by HIV-infected MSM. The natural history of anal HPV infections in MSM may differ from the natural history of cervical infections in women or FSWs (without HIV), respectively. (Micro-)traumata and inflammations delay or impair clearance, and they may also stimulate reactivation of latent infections or infections which already entered the process of clearance, but had not yet completed it, thus stopping or reversing this process. The anal area is prone to micro-traumata and (maybe low-grade) inflammation or even some grade of eczemas, even in the absence of anal sex, and even more in the presence of anal sex. Since the A5298 trial involved mostly HIV-infected MSM, it is probable that many of them practiced anal sex (whether protected or unprotected doesn't matter in the context of mechanical micro-traumata and trauma-induced inflammation).

The cervical area is a much more "protected" area (even in FSWs if they work consistently with condoms) where HPV infections may have the chance to clear with less disturbance and interruptions than in the anal area of MSM. However, this question is still open, and these are only theoretical considerations.

But there is another aspect, and this one is based on studies. SCHIM VAN DER LOEFF et al. consider the A5298 trial as the only trial so far in a heavily pre-exposed population. However, there are vaccination RCTs in young adult women where a substantial portion of the participants were HPV16/18-negative, but HPV16/18-seropositive at the time of the first dose. So this subpopulation among the participants was pre-exposed to an extent of 100 %. According to the results of these prospective studies, summarized and combined in the ARBYN Cochrane review (table 11), the effectiveness of the vaccine in these pre-exposed women was quite good and only a little less than in naïve (or pseudo-naïve) women from the same RCTs. (I call these women "pseudo-naïve": women who were infected in the past, but didn't generate antibodies or the antibodies titres are lost or too low meanwhile, below the limits of detection, so that these women are misclassified as "naïve", but in fact they aren't

truly naïve). The results from the RCTs mentioned in the ARBYN review are confined to the cervical mucosal site. These "cervical" results are thus in contrast to the results from the anal site of the A5298 trial. And the endpoint used in these studies (CIN2+) is of higher clinical relevance than persistent infection. These differences may be explained by differences in the natural history of cervical infections versus anal infections in MSM as discussed above.

Nevertheless, the study design of the A5298 trial, which produced disappointing results concerning persistent anal infections, showed favorable effects with regard to oral infections. This underlines the grade of evidence for these "oral results", in spite of their large confidence intervals.

The second contra argument in the SCHIM VAN DER LOEFF paper is the suggestion that women who once cleared an earlier HPV infection in the past, will also do so in the future. As the authors point out in their paper, vaccination of these women will still have a protective effect for their clients, which attenuates this contra argument a little. I agree that the probability that these women can clear a reinfection of the same HPV type is higher than in women who were not pre-exposed to that type, but there is no guarantee that they will do so. Otherwise, there would be no cases of new infections, new persistent infections or new CIN2+ in the RCTs among those women who were seropositive but HPV-DNA-negative at the time of vaccination, even in the unvaccinated or placebo-vaccinated control group. So, in fact, reinfection (or reactivation) may happen also in women who seemed to have cleared the former infection, and who were able to generate natural antibody titres which reduce the risk of reinfection to some extent, depending on the titre (BEACHLER et al. 2016, see below).

Furthermore, the age-dependent incidence of cervical cancer shows two or even three maxima in different age groups, which may point to a reduction of natural immunity against HPV with increasing age. Since cancer is diagnosed at least 7 – 8 years after infection, and in most cases about 20 years later, the decrease in natural immunity must have started many years before the second and possibly third maximum of cancer incidence (time of diagnosis).

Second, many FSWs are smokers, or intensify pre-existing smoking during sex work. Other FSWs are at first nonsmokers, but started smoking sometime after starting sex work. So even if they were able to clear infections in the past when they were nonsmokers, it is unsure whether they well be able to do so while heavily smoking? Smoking impairs clearance and promotes persistence and progression.

BEACHLER et al. (2016) showed the effects of natural antibody titres and the risk of reinfection (which may, of course, also mean reactivation of a non-diagnosed latent infection). It is clear from these results that women who were able to clear the infection (or to reduce the infection to a latent stage) may suffer from reinfection (or reactivation), and the probability is dependent on the natural antibody titre (as expected). As a consequence, women with cleared infection and low natural antibody titre have a higher risk of reinfection (and may profit more from vaccination) than women with high (> median) natural titres. These effects were also confirmed in an analysis of the Costa Rica Vaccine Trial (BEACHLER et al. 2015). In seropositive (but HPV-DNA-negative) women (18-26 years) at the time of vaccination, the effectiveness of the vaccine against prevalent infections was

high when antibody titres were low; in contrast, those with high natural antibody titres did profit only a little from vaccination. Not all details were discussed in this paper, maybe due to limitations of the length of the article by the journal. If one analyses the data from the tables, it becomes evident that the weak effect of the vaccination in those with high natural titres before vaccination is due to a much smaller basic risk of reinfection (or reactivation) in this group. As expected, high natural antibody titres generate a high-grade (though not complete) natural protection against reinfection (or reactivation?), and in this subpopulation of seropositive women with high natural titres, vaccination offers only little additional effect. In women with lower titres, the risk of reinfection (or reactivation) didn't differ a lot from seronegative women (cf. BEACHLER et al. 2016), and thus the efficacy of the vaccine was close to that in seronegative women.

Theoretically, in HPV-DNA-negative (potentially/probably/heavily) pre-exposed women, a test of seropositivity (as least for HPV 16) and, in case of a positive result, the quantification of the antibody titre, might have some predictive value with regard to the effectiveness of vaccination. However, due to the rarity of high natural antibody titres in a total cohort of women intended to get vaccinated, quantitative antibody testing before vaccination doesn't seem to be cost-effective. And if one considers any pre-testing in (potentially/probably/heavily) pre-exposed women before vaccination in order to improve the quality of the balance of "pros and cons" or the cost effectiveness of vaccination, then cervical HPV(16)-testing is of much greater relevance than qualitative or quantitative antibody testing (however, antibody testing may be recommended to FSWs who want to get the vaccine or are recommended to do so but are unsure whether they got it already in the past. In case of a positive result, i.e. an antibody titre which is indicative of former vaccination, they save the money for vaccination. In such cases, quantitative or semi-quantitative antibody testing is certainly cost effective).

The third contra argument concerns those pre-exposed women who are "pseudo-naïve" according to the definition mentioned above. I think this is not a matter of great concern. As shown in the ARBYN review and the CVT, in young HPV-DNA-negative women with low antibody titres, the vaccine is nearly as effective as in "naïve (+ pseudo-naïve)" women. So why should the vaccine work less effective in pre-exposed women without natural antibodies (or below the limits of detection) compared to those with detectable low antibody titres?

The fourth contra argument is an important one, because the relative importance of latency/reactivation versus true reinfection is understood badly and the prevalence of latency may be actually underrated. But this problem applies to all RCTs with potentially/probably pre-exposed adult women. As far as a high effectiveness of the vaccine (e.g. against prevalent or persistent infections or CIN2+ by HPV16/18) in adult women who were HPV-DNA-negative at the time of vaccination is shown in these RCTs, it doesn't matter a lot whether the vaccine prevented reinfection or reactivation of latent infections. A latent infection which never reactivates probably doesn't progress in the direction of cancer, and since there is no viral shedding during latency, there is also no risk for clients. Some other vaccines which are in development (e.g. against Herpes simplex 2, another infection with some relevance for FSWs) are aimed, beside prevention of primary infections, to suppress reactivation in infected people (HSV 2 doesn't clear and cannot be eradicated from an infected person. Once a person is infected, one can only try to suppress reactivation by antiviral agents or, maybe in the future, vaccination). The same applies to Varicella

vaccination in older people to prevent shingles. Since the HPV vaccine is unable to clear a prevalent infection, it is highly plausible that it is also unable to clear a latent infection. However, if it can prevent reactivation (what is still a matter of debate), it is still "effective" and the question of latency is of minor relevance.

Fifth, the SILVERBERG case-control study is an important one, but there are methodological constraints. As pointed out above, in (possibly/probably) pre-exposed women, an effect of vaccination against endpoints like CIN2+ or CIN 3 cannot be expected prior to 3 or 4 years after the first dose of the vaccine, and the available evidence suggests a cut-off at 4 years after that dose. As has already been done with the final results of the VIVIANE trial (where the participants were comparatively more pre-exposed due to the inclusion criteria and their mean age of 37 years at the time of the first dose than women from the general population, though much less pre-exposed than active FSWs) (WHEELER et al. 2016), one should distinguish between events like CIN2+ or CIN3 which occur in the first ~ 4 years after the first dose (< 4 years) and those which occur later (4 years and beyond). For example, the VIVIANE trial found no reduction of CIN 2+ (irrespective of HPV type) at all in the totally vaccinated cohort (i.e. the cohort including the pre-exposed women) compared to controls within months 0 – 48 (time interval), but 33.8 % in month 48 (point of time). Confined to CIN2+ associated with HPV 16 or 18, the risk reduction was about 80 % at month 48 and also at month 84, so the cut-off is expected to be somewhere between 3 and 4 years (see table below).

Results from WHEELER et al. (VIVIANE trial; eff.: efficacy of Cervarix):

CIN 1 +
0 – 48 months (irresp.*; TVC)**: eff.: 14.8 % (n.s.)
48 months (16/18***; TVCE****): eff.: 75.5 % (n.s.)
48 – 84 months (irresp.; TVC): eff.: **48.1 % (sign.)**
84 months (16/18; TVCE): eff.: **75.5 % (sign.)**

CIN 2+
0 – 48 months (irresp*.; TVC)**: eff.: -1.2 % (n.s.)
48 months (16/18***; TVCE****): eff.: 80.4 % (n.s.)
48 – 84 months (irresp.; TVC): eff.: 33.8 % (n.s.).
84 months (16/18; TVCE): eff.: 78.2 % (n.s., **but nearly sign.,** CI: -13.1 to 98.0)

CIN3+
There are too few cases (0 or 1) for calculations at the time points 48 and 84 months.
0 – 48 months (irresp*.; TVC)**: eff.: none (48 vs. 39 cases among controls)
48 – 84 months (irresp.; TVC): eff.: 67 % (2 vs. 6 cases; n. s.).

Local cervical treatment:
0 – 48 months (irresp*.; TVC)**: eff.: 7.2 % (n.s.) (78 vs. 84 cases)
48 - 84 months (irresp.; TVC): eff.: **61.9 % (sign.;** 10 vs. 26 cases).

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*irrespective of HPV type
** total vaccinated cohort, i.e. irrespective of HPV pre-exposition at the time of vaccination
*** only CIN which are associated with HPV 16 and/or 18
**** total vaccinated cohort for efficacy (excludes women who were pre-exposed to both HPV 16 and 18 at the time of vaccination; pre-exposition like HPV-DNA or seropositivity to one of the two types was allowed; thus, TVC is more inclusive than TVCE and TVC resembles a cohort of potentially pre-exposed women without any testing before vaccination)

The results show obvious differences with regard to vaccine efficacy between 0 – 48 months on one side and 48 months, 48 – 84 months and 84 months on the other side. The study was probably underpowered to find significant differences in all of the categories from 48 months on, which may in part also result from the "old" age structure of the cohort and thus comparatively low risks for events like CIN2+ or treatment needs even in the control group. As shown my McCLUNG et al (2019), in the United States the number of diagnosed CIN2+ (HPV16/18) in women aged 40-44 years (which corresponds to the mean age of the women in the last years of VIVIANE) was about 75 % less than in women between 20 and 29 years at the time when HPV vaccine was introduced and before the first effects on CIN2+ prevalence could be expected in those age groups (year 2008).

The VIVIANE data suggest that in such a (potentially/probably pre-exposed) population a cut-off close to 48 months should be chosen if one wants to identify protective effects of the vaccine for endpoints like CIN2+ or, better, CIN2+ (16/18). Before that point of time, no or only negligible effects can be expected with regard to endpoints of cytological/histological relevance like CIN 2+ because all or nearly all of the CIN2+ which occur during the first 3 years after the first vaccine dose, and many of the CIN 2+ which occur in year 4, will result from HPV infections which were already present at the time of vaccination, especially if HPV status at the time of vaccination is not examined or considered.

The longer the time since vaccination, the higher the relative (protective) effect of the vaccine compared to unvaccinated controls, and the higher the cumulative incidence of events which could be prevented by the vaccine. This is demonstrated very well in figure 2 in WHEELER et al. 2016 ("cumulative incidence of CIN 1+ irrespective of HPV type"), where the number of prevented events increased on a constant rate, starting after about 2 – 2.5 years, without any signs of weakening or saturation towards the end of the study (7 years), so that it is very plausible that the cumulative incidence of prevented CIN 1+ would have continued to increase by the same rate if the trial had lasted longer. It is also plausible that the same applies to CIN 2+ or 3+, though this is not shown in that graph probably due to the smaller number of events and some temporal delay compared to CIN 1+. It is logical that vaccine-induced reduction of CIN 1+ starts earlier than for CIN2+ or CIN3+.

At the time of study examination in SILVERBERG et al., cases (CIN2+ or CIN3+, resp.) and controls had a mean age of 26.3 or 26.4 years, resp. After adjustment, SILVERBERG et al. found a non-significant 15 % reduction of CIN 3+ in those who got the first dose at an age of 21 years and beyond, a significant 41 % reduction of CIN3+ in those who got the first dose at 18 – 20 years, and of 73 % in those who got the first dose at 14 – 17 years, provided that they got three (or more) doses. With one or two doses, the reductions were only 10 % (≥ 21 years), 2 % (18 – 20 years) and 21 % (14 – 17 years).

Another important limitation of the SILVERBERG study is that it refers to all CIN2+/CIN3+ (irrespective of HPV type), and the efficacy of the vaccine might have been much more pronounced if there had been made calculations based only on CIN2+/CIN3+ associated with HPV 16/18 (see, for example, the differences between the "CIN irresp." and "CIN 16/18" categories in the table above with data from the VIVIANE trial).

Taking into account the time span between a new infection (which could be prevented by the vaccine) and the occurrence of CIN2+ or CIN3+ which may result from that infection, what should one expect for those participants who had a mean age of 26.3 or 26.4 years at the time of study examination and who got the first dose at an age of 21 years and beyond (only those who got the first dose during the last six months before study examination were excluded from the study)? Only few of these women will have spent significant longer times than 4 years after vaccination, and those few women may contribute to the 15 % risk reduction of CIN3+ and 8 % risk reduction of CIN2 + in the 3-dose group. It would be very interesting to see results separately for those (among those vaccinated at 21 years and beyond) who got the vaccine less than 3 years ago compared to those who got it 4 years or more ago (assuming a cut-off somewhere between 3 and 4 years), but these calculations where not carried out. Additionally, as already mentioned above, it would be also very interesting to see these calculations (and all results) restricted to CIN 2+ (16/18) and CIN 3+

(16/18). This matters a lot, since CIN2+ (16/18) and CIN3+ (16/18) have a worse prognosis than CIN2+ (non-16/18) or CIN3+ (non-16/18).

Without these missing information and calculations, the results of SILVERBERG et al. are completely in line with what has to be expected from such a study design. However, this study is very valuable because it finally demonstrates that one or two doses of Gardasil are not enough. This was also suggested by former studies, but now it is definitely clear, even with respect to younger age groups beyond 14 years.

Thus, in a retrospective study like that of SILVERBERG et al., it is important to respect thoroughly the time of the first vaccine dose and the time interval between first dose and study examination. If this is not done, this will attenuate the effectiveness of the vaccine in possibly/probably pre-exposed women because of CIN2+/CIN 3 which result from infections which were already present at the time of vaccination.

Moreover, since the cervical HPV status was not established at the time of vaccination in the SILVERBERG study (as a consequence of the retrospective design), it is not possible in such a study to exclude those who were infected at that time, as could be done by CASTELLSAGUE et al. 2011.

The SILVERBERG study, when considered in combination with the results from the RCTs with young adult women as summarized in the ARBYN paper, is thus another argument in favor of HPV(16-)testing of (probably/heavily) pre-exposed women/FSWs prior to vaccination in those cases when there are no extra-genital risks which favor HPV vaccination on their own (e.g., unprotected oral sex risks). For example, there was a 88.7 % reduction in the combined incidence of persistent infections, CIN or extragenital lesions like genital warts associated with HPV 6/11/16/18 after a median time of 4.0 years after Gardasil vaccination in 24 – 45 years old women (age at the time of vaccination) in a RCT for the per-protocol cohort (seronegative and PCR-negative at the time of vaccination; 3 doses) (CASTELLSAGUE et al. 2011). So there is little doubt that those FSWs would profit from vaccination who fulfill the criteria of such a cohort (PCR-negative and seronegative), but, as discussed above, being PCR-negative is much more important than being seronegative since seropositivity in the absence of PCR-positivity reduces the efficacy of the vaccine only to a minor extent (compared to PCR-positivity).

In spite of these limitations (no differentiation between “young” and “old” vaccination, i.e. < 3 or 4 years versus ≥ 4 years; no separate results for CIN2+ and CIN3+ associated with HPV 16/18), which all attenuate the efficacy of the vaccine, the SILVERBERG paper recommends catch-up vaccination for 18 to 20 year old women with 3 doses, so in any way it is compatible with recommendations in favor of vaccination for very young FSWs or young beginners in sex work. Looking at the somewhat disappointing results for this age group (-32 % CIN 2+ and –41 % CIN 3+ following three or more doses), one must recall that these reductions apply to all CIN2+/3+ irrespective of HPV type and that (in accordance with other trials) the reduction quote can be expected to be (much?) higher if the calculation was restricted to CIN2+/CIN3+ associated with HPV 16/18, but the association with special HPV types was not part of the study protocol.

In summary, there is substantial evidence that there is a not very small (but difficult to be calculated) portion of FSWs who may profit only (very) little from vaccination as far as their genital/cervical site (and, per smear infection, their anal site) is concerned. However, since it is extremely improbable that a FSW had been pre-exposed to all HPV types of Gardasil 9, there should be at least a small profit in any case, if Gardasil 9 is chosen for vaccination.

However, the least genital profit can be expected for those who are actually infected by HPV 16. Thus cervical HPV(16)-testing in heavily pre-exposed women like FSWs may have an important predictive value with regard to the effectiveness of the vaccine in that individual case and may improve the precision of the balance of "pros and cons" and also the cost-effectiveness of vaccination.

So SCHIM VAN DER LOEFF's arguments "contra" HPV vaccination are mostly arguments in favor of HPV(16)-pretesting of probably/heavily pre-exposed women (FSWs), and the result of this test should then become an important aspect of the balance suggested in the paper. But as mentioned above, I don't think that HPV(16)-pretesting is recommended in all cases of "adult" or FSW vaccination. I would recommend it only in those cases where it would have a decisive and crucial effect on the balance. As pointed out above, if a FSW likes to perform (or get performed) unprotected oral sex, the balance is in favor of vaccination, independent of genital HPV status. In any case, cervical cancer screening is important for all FSWs (and former FSWs), whether vaccinated or not, and, as pointed out above, the risk of CIN2+ in possibly/probably pre-exposed women stays nearly the same in the first four years after vaccination compared to unvaccinated women. HPV vaccination, for whatever reason it is recommended (e.g. unprotected oral sex), should always be supplemented by information concerning the importance of cervical screening.

In summary, I agree with SCHIM VAN DER LOEFF's paper that the recommendation of HPV vaccination to FSWs should be based on a balanced individual decision and not on a general pro- or contra-statement which applies to all FSWs. However, since I also consider the risks of unprotected oral sex for FSWs themselves as well as for their clients, I see the balance more often in favor of vaccination. But there is also no doubt that the contra arguments the authors present in their paper show important limitations concerning the anogenital effectiveness of the vaccine in (possibly/probably/heavily) pre-exposed women like active FSWs; however, some of these limitations can be overcome if one considers cervical HPV(16)-testing before vaccination in selected individual cases as part of the balanced decision.

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