HPV Prevention and Control Board

Prevention and control of HPV and HPV-related cancers in Denmark: lessons learned and the way forward

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Meeting report

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The HPV Prevention and Control Board convened its first country meeting in Copenhagen, Denmark to discuss the prevention and control of human papillomavirus (HPV) and HPV-related cancers in Denmark. To this end, several country-specific topics were discussed: the Danish healthcare system, HPV epidemiology, burden of disease, surveillance and population-based studies, as well as HPV vaccination and cervical screening, achievements and challenges in Denmark and globally. Finally, the way forward was discussed in five roundtable sessions, each focusing on one of the following questions: How do we define a vaccination success story?; What can we learn for Denmark?; What can we learn from Denmark for other countries with decreased immunization coverage?; What can we learn from Denmark for countries with satisfying immunization coverage?; What is the role of the vaccine industry in a crisis situation?

The meeting was organized as a platform to discuss the current situation, and as such the view of the speakers does not (necessarily) reflect the opinion of the HPV Prevention and Control Board. Meeting presentations referred to in this report are available at www.hpvboard.org.

The Danish healthcare system

Denmark is a small country with a population of 5.7 million inhabitants and a gross domestic product of nearly 55,000 Euro per capita. The Danish healthcare system has a universal coverage, with free and equal access. It is financed by general taxes, and organized with a high degree of decentralization: Denmark is divided in 5 regions, with a total of 98 municipalities. Regulation and coordination are performed at the national level, including the determination of health policies such as vaccination programs. Oversight of general practitioners (GP), hospitalizations, psychiatric care, private practice specialists, adult dental services and physiotherapy are regional responsibilities. Municipalities organize geriatric services, preventive care and health promotion, rehabilitation outside the hospital, treatment of alcohol and drug abuse, and child nursing[1].

The purpose of the Danish national infant vaccination program is to protect the individual against disease, to prevent infection from spreading in society and affect people who are not immunized (e.g. too young), and to contribute to the extinction of severe, contagious diseases worldwide. Vaccinations included in the program are voluntary and free of charge for children under 18 years. The annual cost of the program is approximately 20 million Euros. Criteria for inclusion of new vaccines into the program are: the severity and frequency of the disease; availability of vaccine data in infants/children (e.g. safety data); a positive benefit-risk balance; interactions with other vaccines that may be co-administered and feasibility of integration into vaccination schedules; and affordability. The severity of the targeted disease is given the highest priority when considering introduction of a new vaccine into the program. Vaccines against the following diseases are currently included in the national immunization program: diphtheria, tetanus, whooping cough, polio (poliomyelitis), meningeal infection and epiglottis (Haemophilus influenzae type b), meningitis (pneumococcal), measles, mumps, rubella, and cervical cancer (HPV) [1].

Public health authorities inform parents, day care centers, schools and health professionals about recommendations and benefits of vaccination through publications, folders and campaigns [1].

Despite strong vaccination recommendation of the Danish National Board of Health there has been a substantial decline in HPV-vaccine coverage in Denmark recently. This decline in coverage is linked to reports of a number of women suffering from adverse events that may or may not be related to vaccination. In 2015 the Danish National Board of Health has advised the regions to create a uniform organization of the wards under "One Entrance". GPs refer girls with presumed adverse events to one central hospital ward in each region for uniform treatment and/or guidance. Furthermore, the Danish Government allocated 1 million Euros to research initiatives investigating the possible link between the HPV vaccine and adverse reactions [1].

Epidemiology, burden of disease and surveillance

Epidemiology of HPV and burden of HPV-related neoplasia in Denmark

In Denmark, as in the rest of the world, HPV is the most frequent sexually transmitted infection: more than 80% of adults will have an HPV infection at some time in their lives. More than 200 different HPV types have been identified, of which some 40 have a specific affinity for the anogenital epithelium and 15 types are considered to have oncogenic potential [2]. Nevertheless, most HPV infections are asymptomatic and resolve spontaneously; persistent infection is necessary for high-grade lesions and cancer to develop [3].

In Denmark the overall high-risk (hr-) HPV prevalence in women is 20.5% [4], with peak prevalence detected soon after the start of sexual activity, and gradually declining with age. In contrast, while men have almost the same overall prevalence (17.8% [5]), the peak is later in life and the decline afterwards is less rapid.

The HR-HPV genotypes 16, 31, 51, 52 are most common in women in the general population [4]. These types are also common in penile swab samples obtained from men, with a noted difference being the relatively higher prevalence of HPV 51 compared to HPV 16 in men [5].

For women with normal cytology but with an HPV 16 infection at baseline, the absolute risk of developing cervical intraepithelial neoplasia (CIN)3+ after 12 years is more than 25%, compared to less than 5% in HPV negative women. In this same population, persistent HPV 16 (e.g., HPV 16 detected twice two years apart), the absolute risk is even higher than 45% after 12 years [6]. On the other hand, women with normal cytology and low-risk (lr-) HPV at baseline, have an absolute risk of developing CIN3+ comparable to that among cytologically normal HPV-negative women after 9 years of follow-up [7]. After a diagnosis of CIN3, as a proxy for persistent hr-HPV infection, there is a significantly increased risk for anal, vulvar, vaginal and oropharyngeal cancer, but not for rectal cancer, a form of cancer that is not related to HPV.

Finally, looking at the numbers of HPV-associated cancers and precancerous lesions it becomes clear that men increasingly contribute to the HPV-related disease burden. Assessment of Danish birth cohorts illustrates the reduction in age-standardized HPV-related cancer rates among younger female birth cohorts, likely due to secondary prevention, with a concomitant increase among younger male birth cohorts, likely due to changed sexual behavior [8].

HPV surveillance

Both passive (registry-based) and active surveillance of HPV-related disease are performed in Denmark, contributing real-life data on the impact of HPV vaccination in this population. The use of a unique personal identification number (PIN, consisting of 10 digits with information on birth date and sex) for every citizen in Denmark greatly facilitates database linkage studies using existing population and health-related registries. A similar identification system, using unique PINs, exists in the other Nordic countries (Norway, Sweden, Finland, Iceland), which creates the potential for regional surveillance and/or studies [9]. One example is a long-term follow-up study of individuals who were vaccinated against HPV as part of the FUTURE II study (the phase 3 clinical trial leading to the licensure of the qHPV vaccine), to investigate the effectiveness, safety and long-term immune response to the quadrivalent HPV vaccine [10].

Secondly, the VIP study (Vaccine Impact in Population) was performed in Denmark, Norway, Sweden and Iceland, investigating the occurrence of HPV-related disease before (period 2004-2006, [11]) and after (period 2007-2012) introduction of the quadrivalent vaccine [12]. The VIP study also included the population-based prevalence of HPV infection before and after introduction, based on 2000 liquid-based cytology samples from each country, as well as HPV type distribution in 200 cervical cancers and 300 precancerous lesions (CIN2/3) from each country [12]. Furthermore, a variety of lifestyle and other factors before and after introduction of the HPV vaccine were investigated in women 18-45 years of age including questions on sexual behavior and sexually transmitted infections [12, 13]. Finally, the occurrence of congenital anomalies in babies born to women inadvertently vaccinated during pregnancy was investigated. The Danish data have not yet been published, but an international study is available [14].

Monitoring adverse events following immunization (AEFI)

In Denmark, both healthcare professionals (HCP) and consumers can report AEFI. Healthcare professionals have a legal obligation to report all suspected adverse reactions for new vaccines during the first 2 years post-licensure. After that there is a legal obligation to report serious or unexpected reactions [15]. An adverse event is defined as serious according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [16] and European Medicines Agency (EMA) [17] criteria: an event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

A specific reporting scheme is in place for vaccines, with a focus on batch numbers and other concomitant vaccinations. Reports submitted to the Danish Medicines Agency are forwarded to the EMA, the World Health Organization (WHO) and relevant pharmaceutical companies. Causality assessment is performed for individual adverse event reports, as well as potential safety signals [15].

Within the first year of the HPV vaccine being introduced in Denmark (2009) a comparatively high number of adverse event reports were filed, followed by a decrease in subsequent years. Approximately 10% of the adverse event reports were considered serious. However, from 2013 onwards, the yearly proportion of adverse event reports considered serious increased to 35-55%, mostly reporting persistent incapacity. When reports were ordered according to the year in which the adverse event occurred, a more regular pattern could be observed with approximately 1 adverse event report per 1000 vaccine doses sold, with a slight increase in the most recent years. HCP have filed roughly two-thirds of the reports, while one-third has been filed by patients. Of the adverse event reports submitted by HCP 40% concern serious reports compared to 55% of the reports submitted by patients. The most frequently reported reactions according to the Medical Dictionary for Regulatory Activities (MedDRA) have been nervous system disorders (5,600 or 30%, headache, disturbance in attention, dizziness/syncope, sensory disturbances), general disorders and administration site disorders (3,100 or 16.6%, mostly fatigue), musculoskeletal disorders (2,400 or 13.1%, myalgia, muscle weakness, muscle spasms), and gastrointestinal disorders (2,200 or 11.9%, abdominal pain, nausea) [15]. Due to the nonspecific nature of the symptoms reported causality has been difficult to assess. Following the WHO guidelines for causality assessment [18], most reports fall in the category of insufficient documentation. For an adequate assessment there is a need for review of population-based background data to determine if the risk is higher than expected among non-vaccinated individuals. A potential safety signal was reported to the EMA. After review of the data, EMA communicated that no causal relation was observed for Postural Orthostatic Tachycardia Syndrome (POTS) or Complex Regional Pain Syndrome (CRPS) [19]. Similarly, GACVS did not find any safety issue that would alter any of the current recommendations for the use of the HPV vaccine [20].

Discussion session 1: Medical validation of AEFIs.

During the discussion of the session on epidemiology, burden of disease and surveillance, the medical validation of the AEFIs was questioned. Essentially, all AEFIs are reported, where possible these AEFIs are validated, but this is not always possible, for instance because of long lag times between onset of symptoms and report. Reports two to five years after the onset were not unusual. This makes it more difficult to investigate the temporal relationship between vaccination and symptoms as it creates a risk of recall bias and precludes adequate follow-up.
Denmark has a good system for reporting AEFIs and efforts are undertaken to encourage people to report. The high number of reports may therefore be a kickback of its own success. Given the severity of the events, people want an explanation for the suffering, preferring a biomedical explanation over a potential mental explanation.
The media attention may have played a significant role in the high reporting rates, media coverage spurred reports from the public, as indicated by the fact that more than 50% of the

serious adverse events were reported by the public. The reporting went up, but the number of events reported did not go up. There may also have been a role of social media, as it may have triggered a mass psychological event.
While these reports concern a substantial number of women, the set is still too small to come to firm conclusions. Assessment of causality requires a lot of data, and takes time. World-wide data are necessary, including solid data on background incidences, as it is well-known that background incidences of some of these symptoms are quite high in young girls.
Finally, until the end of 2015 the MMR vaccine was given in the same age group, at the age of 12, but results in hardly any AEFI reports. If both vaccines were given concomitantly, the HPV vaccine is generally suspected by both HCP and the public.
In conclusion, medical validation of AEFIs is difficult, if not impossible, due to frequent long lag times between onset of symptoms and report. Most likely, media attention has played a role in eliciting late reports.

Prevention and control of HPV in Denmark

HPV vaccination programs in Denmark

After the licensure of the quadrivalent vaccine in 2006, population-based vaccination started in 2009 in Denmark, focusing on 12-year old girls (birth cohorts 1996-1997), with a catch-up program for girls born in 1994 and 1995. The vaccine strategy among this population included the receipt of three doses of Gardasil, from the GP [21, 22].

Between August 2012 and December 2013, a second catch-up program targeted women up to 27 years of age (birth cohorts 1985-1992), while a free-of-charge catch-up program for girls born between 1993 and 1997 ended in December 2015. Currently, girls up to the age of 18 years can routinely be vaccinated, using a two-dose schedule for those below 14 years. Finally, in 2016, Gardasil™ (Merck) was replaced with Cervarix™ (GlaxoSmithKline) after a public tender [21].

All in all, the vaccination program has been very successful, with nearly 600,000 girls/women vaccinated at the end of 2015 and coverage rates reaching over 90% in some birth cohorts [23]. Similarly, the catch-up program was also successful, reaching 75-80% of the targeted birth cohorts [21]. Within 10 years of vaccine introduction 20% of the entire female population of Denmark has been vaccinated or approximately 30% of females between 10-64 years old (own calculations using demographic data from http://www.populationpyramid.net/). Unfortunately, the uptake of vaccine dropped dramatically in the 2003 birth cohort to an estimated coverage of 44%. In comparison, for MMR2, which is given at the same age, the uptake was 78%. Although the 2004 birth cohort is still being vaccinated, the uptake of the HPV vaccine was only 18% by October 2016 (i.e. after 10 months of vaccination of this cohort) [21].

Cervical cancer screening programs in Denmark

In Denmark, cervical cancer screening is a regional responsibility. In addition to HPV vaccination, screening is also conducted by GPs and the program is free of charge for women. The screening program uses a call-recall system, but due to linkage of databases only non-

screened women are invited. In 1968 cervical cancer screening was introduced, but until 1983 this was opportunistic screening. In 1983, the first national recommendation was issued: screening of women between 23 and 59 years of age, every three years. In 2007, this recommendation was updated to target women between 23 and 49 years of age, every 3 years and every 5 years for women between the ages of 50 and 65 years. As of 2013, a check-out HPV test exists: women between 60 and 64 years are offered an HPV test, and for HPV-negative women no further screening is recommended [24].

Annually within Denmark, approximately 445,000 cytology samples are taken, 55,000 cervical biopsies performed and 7200 CIN treatments done. In 2012, 398 cervical cancer cases were detected, and 75 deaths due to cervical cancer were reported in 2011 [24].

Of the women who have been diagnosed with cervical cancer, 45% were eligible but did not receive cervical cancer screening in the prior 7.5 years [25]. This non-screened, high-risk group has a high overall mortality and high mortality from HPV-related, non-cervical cancer causes of death [26]. Finally, it has been shown that these non-screened women have fewer contacts with dentists and general practitioners than women who participate in screening [27].
Timely follow-up of abnormal (or unsatisfactory) samples is also a challenge: 15% of women are not followed-up within the recommended time interval, with 4.1% not followed-up within 90 days and 2.2% not followed up within 180 days [28].
Another challenge is the second peak of new cervical cancers in elderly women. This could be due to 1) new HPV infection, 2) reactivation of a latent infection due to a waning immune system, or 3) demographic rather than biological differences: differences between birth cohorts, in which case an ad hoc extra round of screening may be helpful [28].

Finally, a challenge remains regarding the optimal cervical cancer screening guidelines for women who enter the screening system and were vaccinated against HPV as girls. According to current guidelines, these women should not be screened with cytology but rather receive a combination of HPV-based screening followed by cytology triage in absence of better (molecular) tests. HPV-negative women can then be recalled after 6 years. This design will be tested in Trial23, which will start in 2017 in four Danish regions [28].

Self-sampling in Denmark

In Denmark, screening coverage is 75%, but 45% of all cervical cancer cases are diagnosed among the 25% women who have not been screened as recommended (non-attenders) [29]. A qualitative study among 48 women, aged 23 to 39 years, found a number of reasons for non-participation, including some that can be overcome using home-based sampling such as unease with the gynecological examination and problems in relation to seeking a doctor [30].

Three strategies have been, and still are being, tested in different geographic regions worldwide for reaching out by providing self-sample kits to non-participating women: mail-to-all, opt-in, and door-to-door visits. While the mail-to-all was shown to provide better results than the opt-in strategy in a global systematic review, this was not the case for the Nordic countries [31]. Therefore, in 2014 23,632 women not attending regular screening programs, were invited to

participate in the Copenhagen Self-sampling Initiative (CSi). CSi used self-sampling brushes with a novel RFID-chip for secure patient-identification and introduced a variety of communication platforms for participants. Self-sampling was well-accepted among participants. The study recommends the integration of modern technology-based platforms into regular screening programs, allowing easy access for the citizen and reducing the work load in administrating self-sampling approaches (this study was not presented at the meeting, but because of its relevance to the meeting topic it is added to this report) [32].
A self-sampling study CHOICE (Cervical HOme-based CancEr screening, [33]) will be undertaken in the central region of Denmark, coordinated by the Department of Public Health Programs of the Randers Regional Hospital, to compare usual care to usual care with opt-in, and to usual care plus mail-to-all for non-participants in the organized cervical cancer screening program. Each arm will contain approximately 3000 women. The primary aim is to evaluate the effectiveness (participation) of having an offer to obtain a sample at home and the secondary aim is to measure the proportion of women with an hr-HPV infection who receive proper cytological follow-up.
Self-sampling is mentioned as a new strategy in the Danish Cancer Plan IV, which was published by the Danish government in August 2016, aiming to implement new initiatives and priorities based on patients' needs. Self-sampling may also be included in the forthcoming revision of the cervical cancer screening guidelines [30].

Cervical cancer treatment and late effects

The number of cervical cancer cases in Denmark is still comparatively high to the number in other Nordic countries, especially in younger age groups, with a crude incidence rate of 17/100,000 in 25-34 year-olds, and 22/100,000 in 35-44 year-olds [34]. Denmark has concentrated the treatment of cervical cancer in four highly specialized centers, assuring optimal treatment for the patients, with surgeons who see enough patients to maintain their surgical skills. Each center has a multidisciplinary team, comprised of gynecologists, oncologists, pathologists and radiotherapists, amongst others. As part of a national optimization strategy towards improved cancer survival Fast Track cancer referral programs were introduced in 2009. The goal was to limit the time between diagnosis and intervention, i.e. from referral to start of initial treatment only 28 days are allowed for surgery, 31 for chemotherapy, and 35 for radiotherapy [34].
Early stage cervical cancer is mainly identified during cytological screening or by early symptoms in women in their early forties, necessitating advanced surgery with deep dissection in the pelvis. These were primarily performed by total abdominal hysterectomy, but since the introduction of robotics there is a transition to minimally invasive surgery. Even using robotics, late stage effects after surgery frequently occur: 30% of patients have difficulties emptying the bladder 2 years after surgery, there is an increased risk of sexual dysfunction the first 6 months after surgery, and approximately 10-25% of patients have varying degrees of leg lymphedema [35]. The late stage effects after radiochemotherapy can be more severe [36]. To illustrate this a case study was presented: a 31-year-old woman with a localized cervical tumor without lymph node metastases was treated by robotic assisted surgery. Due to the presence of significant risk factors after surgery, this woman was treated with adjuvant radiotherapy and chemotherapy. At 3 months follow-up, the PET CT scan was suspicious. A repeated PET CT at 5 months and

gynecological examination under general anaesthesia confirmed a local recurrence in the radiation field. This was followed by a complete exenteration with two stomas; the 5-year survival prognosis is estimated at 30-50%. This woman was outside the age group that was offered HPV vaccination, and she had two negative Pap smears before she was diagnosed with cervical cancer [34].

This case study illustrates that while hi-tech equipment and state-of-the-art procedures are applied, and the 5-year survival rate increases slowly but steadily, this is not a guarantee for successful treatment. Therefore, as cervical cancer remains a vaccine-preventable disease, the best way not to die of cervical cancer is to be vaccinated [34].

Discussion session 2: Impact of vaccination on screening

HPV DNA-based screening is more sensitive and will lead to a higher negative predictive value. However, this will create the need for a triage method. Data from Scotland, where vaccinated women are entering the screening system, showed that cytology as triage is good, but not perfect. Molecular tests need to be developed to provide better solutions.

Furthermore, the impact of the decreased vaccination coverage rate on herd protection in Denmark was discussed. Coverage rates below 50% will not provide a herd effect, but the Danish situation is special due to the high coverage rates of the recent past. It was suggested that it should be possible to model the increased burden of disease as a consequence of the decreased coverage, including the impact on boys, and communicate this to parents, to show the benefits of vaccination.

Achievements and challenges in Denmark and lessons learned

The case of POTS

A total of 782 patients with an average age of 23 (range 12 - 73 years) were referred for possible side effects of HPV vaccination to one of the 'One Entrance' clinics in Denmark. Of these, 689 were seen, and the main symptoms observed in these patients were: orthostatic intolerance, headache, fatigue/fatigability, nausea/abdominal pain, dysaesthesia, and involuntary muscular contractions. Around 50% of these patients presented with symptoms that fitted the POTS definition. Over 60% of these patients had a physical activity level that was well above average [37, 38].

Care-seeking in females reporting severe adverse reactions to HPV vaccine

What has come to be known as "the Danish signal" consisted mainly of medically unexplained physical symptoms (see section above) in girls, occurring soon after HPV vaccination [39]. So far, only few studies have looked at non-specific outcomes, and found no increased risk of these symptoms among vaccinated versus unvaccinated girls [40, 41]. Donegan et al. [40] performed near-real time 'observed vs. expected' analyses comparing the number of reports of fatigue syndromes submitted via the MHRA's Yellow Card passive surveillance scheme to the expected number, using background rates calculated from the Clinical Practice Research Datalink and estimates of vaccination coverage. The number of spontaneous reports of chronic fatigue

following HPV vaccination was consistent with estimated background rates even assuming low reporting [40].
However, these unexplained physical symptoms are difficult to analyze in epidemiological studies, as the conditions are ill defined, and without clear ICD-10 codes.

Of the criteria described by Hill in 1965 [42] to investigate causality, temporality (effect occurring after the cause) was chosen to assess the suggested causality between the symptoms described and HPV vaccination. A case-control study was performed by the Statens Serum Institute, comparing 361 women who reported SAE following HPV vaccinations to the Danish medical authority with 164,000 female controls matched on municipality, age and year of first HPV vaccine dose. Care seeking data were retrieved from the national health insurance service register for primary care data, and the national patient registry for hospital contacts. A bimodal age distribution was found among the cases, reflecting the successful HPV catch-up vaccination program in Denmark. Although no difference was found in the number of consultations, in the two-year period before the first HPV vaccination, the cases more frequently consulted the GP by phone or e-mail, had more laboratory analysis requests, and more frequent physiotherapy and/or psychologist appointments. In contrast, contacts with the dentist were similar between cases and controls [23]. Similarly, before vaccination, cases had more frequent hospitalizations for a range of conditions including those related to the digestive and musculoskeletal systems and injuries [23], suggesting that the effect did not occur after the intervention, making it less likely that the symptoms are true adverse events.

Progress achieved – real world impact from a Danish perspective

To fully appreciate real-life data, a distinction must be made between overall impact assessment of HPV vaccination in a population independently of vaccination status and vaccine effectiveness in a population including information on vaccination status on the individual levelEarly HPV-related outcomes (HPV prevalence, persistence, genital warts), mid-term outcomes (CIN, precancer) and late outcomes (cancer incidence, mortality) can be observed. As an early outcome, HPV vaccine impact has been observed for the reduction of genital warts, with a significantly decreasing incidence of genital warts in women up to the age of 35 and in men up to the age of 29, indicating substantial herd protection [43]. Within Denmark it is possible to identify individuals who received an HPV vaccine through the National Health Service Registry (for those vaccinated through the national program) and the prescription register (for those vaccinated outside of the national program). Using these data, as well as information on all prescriptions on topical medicine for genital warts, as well as information on admissions and out-patient visits for genital warts, the effectiveness can be investigated. In total, data from 248,403 vaccinated girls were investigated. The relative risk of genital warts among girls who had received at least 1 dose of vaccine compared with unvaccinated girls was 0.12, 0.22, 0.25, and 0.62 for those born in 1995-1996, 1993-1994, 1991-1992, and 1989-1990, respectively (P for trend < 0.0001). No genital warts occurred among vaccinated girls in the youngest birth cohort (1997-1999) [44, 45].

Similarly, population impact has been shown for cervical precancerous lesions, where a strong decrease in the number of CIN2+ cases was shown in the 18-20 year age group after

introduction of vaccination. A reduction, albeit less spectacular, was also seen in the age group 21-23, whereas no effect of vaccination on CIN2+ was observed in women older age groups[46]. As in the clinical trials [47, 48], the smaller risk reduction of CIN2+ in the older birth cohorts was probably because of a higher prevalence of HPV16/18 infection before vaccination.

Similarly, in a study of effectiveness using data from the national pathology databank, a significantly decreased risk for CIN2/3 could be observed in the birth cohorts 1991-1992 and 1993-1994 [49]. For younger birth cohorts it is too early to see an effect, although a decreased risk for early HPV-related outcomes such as atypical squamous cells of undetermined significance (ASCUS) could already be observed in the 1995-1996 birth cohort. From these data it could also be observed that an equal effect between 2 doses and 3 doses is achieved when the interval between the 1st and the 2nd dose is 4 months or more, in women who were 16 years or younger at vaccination.

Evidence-based general practice: prevention among healthy people

For any medical intervention there is a balance between benefits and risks [50]. This is even more evident for vaccines as they target healthy populations and coverage can be quite broad. Continuous evaluation of risks and benefits of vaccination is required to strengthen the confidence in immunization programs. A careful benefit/risk assessment is obliged to: (1) address the population at risk (not the individual at risk), (2) take into account contextual issues (economics, availability of alternative vaccines, sociopolitical and cultural factors), (3) Be prompted by a newly identified risk, yet remain holistic (e.g. take into account the entire safety profile of a vaccine, not only the specific information relating to the event that was detected), (4) Run in parallel to active enquiry, cooperation and exchange of information [51].

Danish Cancer Society initiatives and the background for the initiatives

The Danish Cancer Society (DCS) aims to prevent the development of cancer, improve patients' chances of successful recovery, and limit the physical, psychological and social side effects of cancer through research, patient support, and prevention. The DCS has 430,000 members and 45,000 volunteers. At the introduction of the HPV vaccination program, DCS held a campaign focusing on mass media, a website and network campaigns. After the media crisis in 2013 DCS developed a communication plan with the objective to return to a vaccination coverage of 80%, by being clear and trustworthy, facilitating a sound and relevant debate, and providing relevant and reliable information to parents. DCS started a dialogue with the media, presenting general information and case stories, developed speed drawing movies with information about safety and efficiency of HPV vaccination, and started a dialogue with vaccination opponents and doubters. Finally, a Facebook account was opened providing information and room for an online dialogue. However, due to fierce debate and a flood of negative reactions, this account was closed in December 2015. As the vaccination coverage continued to decline further studies were undertaken to obtain insight into the reason for not vaccinating. These studies showed that parents are scared by the media reports on unexplained symptoms, and many feel that the risk of adverse reactions is higher than the risk of getting

cancer. Parents lack information about the adverse reactions and cervical cancer, but only 4 in 10 ask their GP for further information. Nevertheless, some parents indicate that they may have their daughters vaccinated at a later stage. Therefore, the 2017 campaign will be aimed at dealing with the ”post factual society”, improving communication on social media, communicating the new data on effectiveness and safety, and getting GPs more involved [52].

Danish Health Authority: possible efforts to increase HPV vaccine uptake

The public debate on HPV vaccination is dominated by safety concerns, with a key role for social media, including several groups on Facebook for girls with suspected HPV vaccine side effects. The subsequent declining vaccine coverage is a public health concern. A study performed in cooperation with DCS showed that 52% of parents support vaccination, 14% oppose to vaccination and 34% of parents are in doubt. This latter group is less knowledgeable and in doubt about essential facts, understands the risk of cervical cancer but not the relative risk in relation to side effects. Furthermore, these parents were positive initially, but became hesitant after the media attention. Finally, this group has highest confidence in the DCS and the Statens Serum Institute, as well as their own GP, but also trust the patient organization for girls experiencing side effects. The parents want to be convinced but are awaiting more information. These parents may be convinced by providing statistics on the risk of cervical cancer compared to the risk of side effects from HPV vaccination. The message may be strengthened if it comes from a joint voice from authorities. The parents should be referred to their GPs for clarification and advice. Finally, parents need to be convinced that girls can be infected with HPV at sexual debut, therefore, postponing the decision about vaccination increases the risk to become infected.

Discussion session 3: Influence of the public response on vaccination achievements

As the presentations on ‘the case of POTS’ and ‘evidence-based general practice’ met with considerable disagreement, the discussion was started by restating a few facts:

- Cervical cancer is caused by infection by hr-HPV, especially the types 16 and 18
- Almost all high-grade pre-cancers are caused by one of those hr-HPV types
- Vaccination of individuals not yet exposed to the virus, prevents infection (if not disease), as can be concluded from the Australian data
- Regarding the secondary intervention, no RCTs are available, for historical reasons, RCT were not the Gold standard at the time, not an ethical thing to do.
- If CIN3 is not treated with standard of care, approximately 50% over a 30-year period will progress to cancer (based on data from an unethical study performed in New Zealand).

Given the high vaccine coverage rates in Denmark, exposure to the vaccine is a very common exposure: some 600,000 of Danish girls/women have received the HPV vaccine. If some of these girls develop an uncommon disease, this does not automatically imply a causality. This situation was referred to as the McDonalds syndrome, a large proportion of the population will visit McDonalds at one time or another, but this does not mean that the suspected infection that is detected afterwards in a subset of this population is due to that visit. The types of disease that most often draw the attention of the anti-vaccine activists are uncommon neurological or multifactorial immunological diseases, with unclear symptomatology. In addition, the very

powerful emotional outcry from the anti-vaccine activists is not matched by the low-key, evidence-based response by those who defend the vaccine. However, this has to fit in with the local culture; when Danish mothers were asked for their preferred response, they chose a scientific response over an emotional response.
The question was raised how it can be explained that these symptoms are seen in some countries such as Denmark, Ireland and Japan, but not in other countries with high coverage rates and excellent surveillance systems such as Australia, Scotland and some other Nordic countries,even the population is not that different from that in Denmark. Can this in part be due to the very successful catch-up program in Denmark, which targets a different age group, potentially more prone to these events?
Over 99% of the women vaccinated do not have any side effects, other than a temporary sore arm. Large RCTs have shown the vaccine efficacy and safety, large phase IV trials have been performed to investigate pharmacovigilance, and the benefit risk balance. Nevertheless, side effects can still occur, such as narcolepsy in pandemic influenza vaccination and intussusception in rotavirus vaccination. This only shows the importance of good (post-marketing) surveillance.
Once a crisis occurs, the most powerful reaction is obtained when all HCPs, including pharmacists and nurses, form a single front, with clear, united and culturally appropriate responses, including clear messages on the benefits of the vaccine and the challenges of cervical cancer. Hold steady to the evidence we possess. Perhaps not all HCP are appropriately trained to support the girls and parents who have questions.
Finally, today, social media cannot be ignored, including Facebook and YouTube. Data show that the decision to vaccinate is formed by the mother, and they are (still) on Facebook. For some people Facebook is the single most important form of information. Navigating on social media is not simple for vaccine supporters, as they are likely to meet ‘shit storms’, loads of negative, emotional responses, without any scientific basis. But it is an essential medium to communicate with the public.
In conclusion, only a small minority of vaccinated women will experience side effects. While these women need to be treated in the best possible way, the occurrence of these side effects should not negatively impact the use of a safe and effective vaccine with a positive benefit risk balance.

Global achievements and challenges

HPV Programs at a global level

Worldwide, 67 countries (35%) have introduced HPV vaccination and these are generally not the highest risk countries, which are located in Africa and Asia.
The global HPV vaccination coverage is below 15%. There are approximately 60 million girls in each birth cohort, with over 60% residing in one of 15 countries: Bangladesh, Brazil, China, Democratic Republic of Congo, Egypt, Ethiopia, India, Indonesia, Mexico, Nigeria, Pakistan, Philippines, Russian Federation, Tanzania, and the USA. Of these, only four have an HPV vaccination program: Brazil, Mexico, Russian Federation, and the USA. Furthermore, only eight countries worldwide vaccinate men.

In general, a slow progression is observed from successful Gavi, the Vaccine Alliance, demonstration projects to national introduction of HPV vaccination. Diverse settings for the delivery of the vaccine are available such as school or practice-based, or a combination of the two. For each country, the most cost-effective vaccination setting needs to be determined, keeping in mind that high coverage rate can be obtained with each of these settings. In fact, increasing coverage rates since introduction are observed in most countries.
The WHO provides support for policy and decision-making as well as in planning and implementation of vaccination programs. Nevertheless, global uptake of HPV vaccination remains slow in, mainly reaching girls in lower-risk countries [53].

What can we learn from hepatitis B vaccine and other vaccine safety issues?

The hepatitis B (HepB) vaccine is an excellent example of the damage that unsubstantiated rumors can do to vaccination programs. The initial HepB vaccine was derived from plasma at a time AIDS was first discovered, but the causative agent was unknown. It was suggested that AIDS could be transferred through the vaccine. Once HIV was discovered it was proven that it was not present in the vaccine, but vaccination programs did not recover until the development of DNA recombinant vaccines in 1986 [54].

Like HPV, Hepatitis B (HBV) can be sexually transmitted, therefore, the initial recommendation was to focus vaccination on high-risk groups: health care professionals, sex workers, men having sex with men, and patients with sexually transmitted infections. While this strategy protected individuals, it failed to decrease rates of disease. Nowadays, more than 90% of countries use HepB vaccine universally, with global coverage rate of 83% (2015).

In 1996, it was reported in France that multiple sclerosis (MS) occurred more frequently in patients who had received HepB vaccine (described in [55]). This was picked up by anti-vaccine groups and political pressure led to a suspension in France of the adolescent vaccination program and severe damage to the infant program. The WHO and the Viral Hepatitis Prevention Board (VHPB) quickly convened an “expert meeting” to examine the evidence and issue their findings [55-57]. Furthermore, the method of the initial French investigations, using data from reported cases, attempting to compute relative and attributable risks using adult Td vaccine as a comparator, was criticized [58]. The investigators made errors in assumptions about the data, including inappropriate use of controls and inappropriate application of epidemiology, rendering the conclusions invalid. Passive reporting data should be analyzed with care and used only for hypothesis generation - anything more requires robust epidemiological study [58]. Unfortunately, the damage to the French program persists to this day with very low rates of both infant and adolescent coverage, although the infant coverage is on the rise with the introduction of the hexavalent vaccine. To this day French courts are awarding damages for MS caused by HepB vaccine.

Similar HepB vaccine safety concerns occurred in Vietnam in 2007 and 2013, and in China in 2015. Media rapidly report rumors of deaths due to vaccination, whereas governments are slow to investigate reports. The resulting damage to vaccine coverage can take years to recover. After the suggestion of the relation between measles vaccination and autism (publication retracted by

Lancet, author exposed for fraud) it took 12 years in the UK to recover confidence in the MMR vaccine (Figure 3)

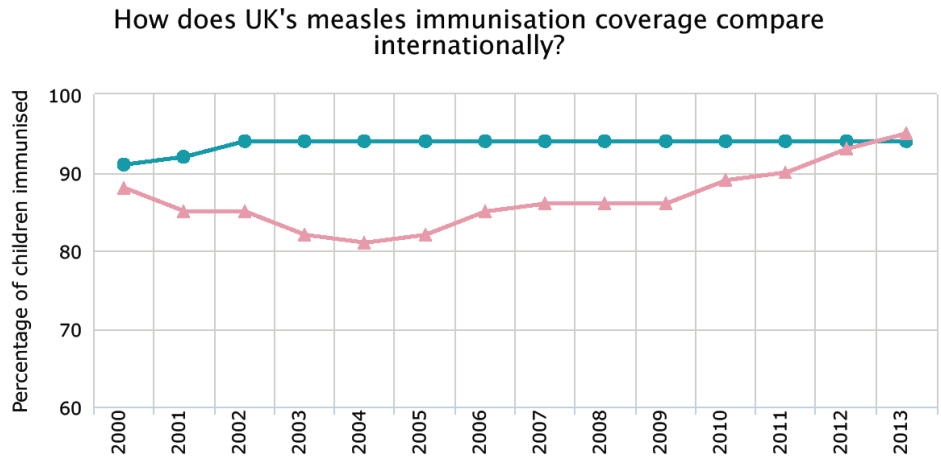

Figure 1: MMR vaccine coverage.

Magenta: Australia, pink: United Kingdom
Source: Mark Kane. What can we learn from HepB vaccine and other vaccine safety issues? [54]

What can be done to prevent/tackle further safety issues? Governments are advised to train all who are involved in vaccination in how to respond to vaccine safety concerns to the public and the media. Most AEFI concerns are not new and have been thoroughly disproved in the past. The AEFI data need to be explained to media and public. The response to alleged side effects should be rapid, with a bold defense of immunization programs from the government. It is therefore of essence to be ready and able to show benefits of immunization and the individual harm of damage to the vaccination program. Finally, communication about HPV should be focused on cancer, not on sex [54].

Discussion session 4. Approaches to improve vaccination rates and impact

The discussion started with the statement that concern of side-effects of vaccination is of all ages. It is feared that the problems in Denmark will affect other regions in the world, leading to a hesitation to introduce the vaccine in countries where cervical cancer incidence is generally higher than in countries where the vaccine has already been implemented. Similarly, it was mentioned that in countries without cervical cancer screening, HPV vaccination is even more important as there is no fall back mechanism to detect lesion at an early stage.

As HPV not only causes cervical cancer, but also a range of other cancers, it also affects boys and men. So far we only see indirect protection, but gender-neutral HPV vaccination will directly protect men. The first results of the introduction of population-based gender-neutral HPV vaccination in Austria are eagerly awaited to see what we can learn from the Austrian approach. Moreover, gender-neutral vaccination is also more resilient to crises. Finally, in communities where sexuality cannot be discussed, gender-neutral vaccination may be a solution to the problem.

The pros and cons of using the example of the lung cancer approach, i.e. the use of confronting photos and phrases on cigarette casings, were discussed. Given that the numbers of cervical

cancer cases are too low to impress, would it be helpful to use pictures of cervical cancer, as people need to understand the consequences of abstaining from vaccination. However, this is culturally sensitive, and definitely does not work at a global level.
In conclusion, while several approaches were discussed, gender-neutral HPV vaccination is likely to be the most successful approach at the global level.

The way forward

To discuss the way forward, five roundtable sessions were conducted, each focusing on one of the following five questions:

- How do we define a vaccination success story?
- What can we learn for Denmark?
- What can we learn from Denmark for other countries with decreased immunization coverage?
- What can we learn from Denmark for countries with satisfying immunization coverage?
- What is the role of the vaccine industry in a crisis situation?

A wealth of ideas were reported from the sessions, an overview of which is provided below.

The definition of successful vaccination depends upon the perspective of the observer. High-level indicators of success, as utilized in public health, include population-level coverage, impact, and trust in the vaccine. At the individual level, an information asymmetry exists: while successful vaccinations are rarely mentioned, risks (perceived or real) are a focus of discussion.

A vulnerability of vaccination programs is that they often react too slowly to reported risks, lowering their chance of success. In all programs, including those that currently reach high coverage, events leading to waning vaccine coverage need to be investigated, and crisis plans with risk scenarios put in place to ensure a timely, effective response in the event of a crisis e.g. rumors.

When considering how risks could be mitigated after a crisis, it was considered that in Denmark, strong clear messages may be perceived as authoritarian, creating further resistance. Participants emphasized the importance of engaging networks of healthcare professionals as they are perceived as independent and without conflicts of interest with industry. It was suggested that public speaking and social media were appropriate communication channels. It was also noted that politicians should be well-informed. The importance of vaccine program leaders knowing and providing tailored information to relevant stakeholders was stressed. It was considered that allocating some of the vaccine program budget to communication and training would strengthen program implementation.

Participants considered that solving crises was more often a communication than a scientific issue, and observed that people are more likely to be convinced by emotional appeals than by scientific evidence. As an ill-informed media is likely to amplify any issues that may arise,

participants recommended early stage media involvement, particularly the timely provision of information to media owners and editors who determine published content. It was suggested that provision of training to the media may decrease the publication of misinformation.

Participants also considered that teachers would also benefit from training (particularly in countries with school-based vaccination), as would HCPs as they are frequently the first line of contact for the public on vaccination. It was proposed that the best strategy to train HCPs would be through introducing training in MD and Pharmacist curricula.

In general, there is a slow response to crises, partly due to a global leadership problem. This problem might be solved by creating a focal contact point at the WHO, or better still, a rapid response team. Any response to issues would benefit from one voice; contradicting messages from HCP will further confuse both parents and girls. In these responses it is better to discuss the positive sides of vaccination, and avoid negative campaigning.

It was suggested that a focus on gender-neutral vaccination may help, but that this needs careful planning, especially in times of crisis. At the same time, lowering the vaccination age to 9-10 years may help to remove the association of the vaccine with sexual activity, while reducing the chance of psychogenic events.

There is a clear role for the industry during crisis: the pharmaceutical industry has data, expertise, and early alert systems. Furthermore, they can provide unrestricted grants for investigator-initiated research. Their involvement is, however, often negatively perceived: the pharmaceutical industry is seen as commercially driven with too much focus on the product and not enough on immunization. It should be carefully explained that: 1) development of new vaccines (and/or drugs) comes from private funding and governments cannot bear the costs of development; 2) the pharmaceutical industry shows increasing transparency, as shown for instance by open access to RCT data; and 3) the pharmaceutical industry welcomes strict guidance, as this makes it clearer how to maneuver.

Concluding guidelines

Based on the discussions of the meeting, several guidelines are suggested:

- Include a communication budget at the start of (national) vaccination programs;
- Consider the use of social media as part of the communication strategy;
- Provide training to HCP on how to discuss the vaccine with vaccinees and their parents;
- Develop a crisis action plan before the introduction of vaccination, as there will be no time once a crisis occurs;
- Define the right age for vaccination, as this may diminish some challenges;
- Communicate about the vaccine as one voice among experts;
- Take potential side effects seriously, but without focusing on the alleged link, keeping the focus on the positive benefit risk balance of the vaccine.
- Reach out to silent supporters of the vaccine

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