Prevention and control of human papilloma virus in Denmark: Lessons learnt and the way forward

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HPV Prevention and Control Board

www.hpvboard.org

Objectives of the meeting

1. To provide an overview of the health care systems and vaccination programs.
2. To review the epidemiological situation of human papillomavirus (HPV) infection and related diseases.
3. To give an overview of the current prevention and control measures on HPV.
4. To discuss the progress achieved in HPV prevention.
5. To review the possible implementation of new prevention strategies, control measures and monitoring systems.
6. To discuss the successes, issues and barriers to overcome, and the way forward.

Introduction (Nedret Emiroglu)

- The World Health Organization (WHO) wants to provide informed advice, in all decisions.
- All policies to implement vaccination are in place.
- 29 of 53 European countries have introduced HPV vaccination
- Denmark (and Ireland) initial success story, with recent drop in coverage due to communication crises.
- More scientific evidence needed, however, the Global Advisory Committee on Vaccine Safety concluded that there are no safety issues to alter recommendation.

Danish health care system (*Camilla Rosengaard Villumsen)*

- Public system, with free & equal access.
- National level -> vaccine program.
- Regional (5) level -> run the system (General Practitioners [GPs] vaccinate!).
- Local (98) level -> elderly care / prevention / abuse / child nursing.
- Debate with the public / patient organizations.

Danish health care system (*Camilla Rosengaard Villumsen)*

- Statens Serum Institute (SSI) and the Danish Board of Health monitor the vaccination program and surveillance of infectious diseases.
- The Danish Medicines Agency (DMA) monitors safety.
- Criteria for introduction of new vaccine: severity / frequency / benefit-risk (BR) balance / interaction other vaccines / money.

Danish health care system (*Camilla Rosengaard Villumsen)*

- Building confidence – trust in health authorities and in the vaccines.
- Efforts to inform patients – folders, campaigns.
- Challenges: ‘one entrance’; one central regional ward for uniform treatment and/or guidance of girls with presumed adverse events.
- Research 1 M euro to investigate link Postural Orthostatic Tachycardia Syndrome (POTS) and HPV vaccine.

Epidemiology of HPV and burden of disease (*Susanne Krüger Kjær)*

- Prevalence of high-risk HPV +/- 20% in women.
- Clear relationship with age, early peak. Second peak found in high-risk countries.
- Prevalence in men +/- 18%, later age pattern, stable or continuously increasing pattern.
- Genotypes 16, 31, 51, 52 most common in women, in men type 51 higher than 16.

Epidemiology of HPV and burden of disease (*Susanne Krüger Kjær)*

- If HPV16+ at baseline, 25% risk of developing CIN3+ after 12 years.
- If HPV16+ twice, risk increases to +/- 50%.
- HPV negative = low risk; low-risk HPV also low risk, ignore in screening.
- Previous CIN3+ related to higher risk for anal, vulval, vaginal and oropharyngeal CA, but not for rectal CA.

Epidemiology of HPV and burden of disease (*Susanne Krüger Kjær)*

- Screening lowers mortality, but still considerable morbidity.
- HPV detection used for triage and follow-up after conisation.
- HPV vaccine prevents HPV infection.
- Both men and women affected by HPV, decrease in women (due to screening), increase in men.
- More prominent when looking at birth cohort, men approaching levels in females.

HPV surveillance (Christian Munk)

- Unique personal registration number helps in follow-up.
- Long-term follow-up in +/- 2750 vaccinated women.
- Effectiveness.
- Safety.
- Immune response.

HPV surveillance (Christian Munk)

- VIP study: Vaccine impact in population.
- Pre- vs post- incidence of cancers.
- Pre- vs post- type distribution (both general and in cancers).
- Pre- vs post- genital warts.
- Post-vaccination sexual habits.
- Post-vaccination congenital abnormalities.

Monitoring Adverse Events Following Immunisation (AEFIs, *Line Michan*)

- First 2 years obligation to report all adverse events (AEs).
- >2 years, only SAEs.
- Large numbers of SAE reported in 2013 and 2015.
- Most reports in 2015 were old (media attention?).
- Healthcare professionals (HCP) report 2/3 of AEs of which 1/3 serious.
- Patients report 1/3 of AEs of which more than 50% serious.
- Mostly long-term incapacitating.

Monitoring AEFI (*Line Michan*)

- Multiple reactions/report (up to 150 reactions/report).
- Unspecific symptoms – causality difficult to assess.
- Set too small – world-wide data needed.
- Quarterly updates provided to GPs.

Discussion session 3

- VIP study: Ecological design, expected uptake of vaccination high, more recent data make it possible to compare vaccinated vs unvaccinated.
- How are AEFIs medically validated : everything is reported, validation is always tried but not always possible.
- Other vaccines are given in the same age group, do similar things occur in girls with other vaccines? MMR in same age group, at age 12, almost no reports. If both are given and AE occur, mostly HPV is suspected.

Discussion session 3

- Rates of cervical cancer (CaCx) are high in Denmark, triple of those in Finland. Difference in habits that increase CaCx, i.e. no. of partners. The rate in Denmark is just below that in Eastern European countries.
- Adjustment for year showed more constant numbers, any bias found? Media make people recognize that there may be a link. Still, could be a genuine side effect, not recognised at the time, only after attention in media. Reporting went up, not the number of events.
- Has social media been monitored? From an anthropological point of view – mass psychological event?

Discussion session 3

- What are the incentives for the public to report AEFI? Compensation system independent from reporting, no economical incentive, no payment for HCP to report, genuine concern, potentially misled by media. How do people know how and where to report? Good system, big effort to encourage to report. Kick-back of own success.
- High reporting explained by severity of illness, people want explanation for the suffering, are highly educated, have high access to internet. Search for biomedical explanation for disease, rather than mental. Sociological, cultural perspectives.

HPV vaccination programmes in Denmark (*Palle Valentiner-Branth)*

- Highly successful catch-up program, 75-80%.
- Steep decline in 2003 cohort – 44%.
- In contrast, MMR in same cohort 78%.
- Still, 20% of total female population vaccinated.
- Ireland and Japan show similar trends.

Cervical cancer screening programmes in Denmark (*Elsebeth Lynge)*

- 1968-1983 - opportunistic screening.
- 1983 – national recommendation.
- 2007 – 23-49y every 3y; 50-65y every 5 y.
- 2013 – 60-64y checkout HPV test.
- Invitation only to non-attenders.
- 25% not screened after 2nd invitation.

Cervical cancer screening programmes in Denmark (*Elsebeth Lynge)*

Second peak in older age group:

1. new partner
2. reactivation
3. demography, difference in birth cohorts

- If 3, extra round of screening.

Cervical cancer screening programmes in Denmark (*Elsebeth Lynge)*

- Screening adaptation to vaccination.
- HPV detection.
- HPV neg –> repeat after 6y.
- HPV pos –> triage by cytology.
- Trial to start in 2017 in 4 regions.

Self-sampling initiative in Denmark (*Berit Andersen*)

- Terminology:
  - Home test – direct answer (i.e. pregnancy test).
  - Home sampling – preferred term.
- Clear instructions needed.
- Reasons for non-participation:
  - Gynaecological exam.
  - Problems seeking a doctor.
  - Practicalities.

Self-sampling initiative in Denmark (*Berit Andersen*)

- Study/
  - Usual care.
  - Usual care plus opt-in.
  - Usual care plus test kit sent.
- +/- 3000 women per arm.
- Evalyne brush plus first void urine.
- 1. aim – participation.
- 2. aim – follow-up (FU) after HPV+ result.
- Results expected in 2017.
- Self-sampling mentioned in Cancer plan IV.

Discussion session 4

- Comment(C) – utilitarian perspective, also ethical perspective; informed choice is by-passed, need to inform on BR. Approach not justified, to be discussed openly. Answer(A) - Denying women an investigating that may prevent them from dying from CA. Harm as in benefits and unintended harms, women need to be informed on these, by law. Always stressed in all offers that it is a personal decision, no force to do anything. BR well communicated in DK. Clear option to opt out.
- Question(Q): How will vaccination affect predictive value of screening? A1: HPV detection more sensitive, higher predictive value. Need for second sorting mechanism, triage method. Probably cytology. A2: Scotland; vaccinated women in screening. Cytology is good, not perfect. Molecular solutions are being developed.

Discussion session 4

- Q: How is brand of vaccine chosen? A: Regular tenders, criteria for decision unchanged, so decision on price.
- Q: What about herd immunity now the coverage has gone down? A: Coverage below 50% will not give herd effect, however, Danish situation is special, question for modellers, or wait for results.
- Q: Experience that women are often afraid of doing sample taking themselves, is this also true for DK? A: Study should accumulate some data, not available yet.
- C: It should be possible to model the preventable burden of disease as a consequence of low coverage and to communicate to parents, also for boys.

Cervical cancer treatment and late effects (*Pernille Tine Jensen)*

- 4 centres for CaCx treatment, assuring optimal treatment with surgeons who see enough patients
- Multidisciplinary group
- Cancer packages: from referral to surgery in 28 days
- Minimally invasive surgery
- Late stage effects after surgery
- Even worse after radio chemotherapy
- Despite all hi-tech equipment and procedures still CaCx
- Therefore HPV vaccine coverage needs to go up again

The case of POTS (*Jesper Mehlsen*)

- Nocebo effect or non-specific effect of vaccine?
- Non-specific effect can be beneficial -> BCG.
- Non-specific effect can be harmful -> DTP.
- 782 referred patients, average age 23 (12-73).
- Wide range of symptoms.
- 50% of girls fit POTS definition.
- High activity level pre-POTS.

The case of POTS (*Jesper Mehlsen*)

- Agonistic autoantibodies found (many other diseases such as Graves).
- Provides rationale for treatment.
- First aim: help these women, whether or not associated with HPV vaccine.

Care-seeking in females reporting SAEs after HPV vaccination (*Kåre Mølbak*)

- Conditions ill-defined, no clear ICD-10 code.
- Hill's criteria -> temporality investigated.
- Case-control study on 361 patients.
- Bimodal age pattern, due to catch-up.
- More frequent healthcare contacts before vaccination in women with POTS.
- Still need to know why these women are ill.

Progress achieved, real-life data (*Susanne Krûger Kjaer*)

- Impact (mix of vaccinated & unvaccinated).
- Impact shown on genital warts (GW) and cervical intraepithelial neoplasia (CIN)2+.
- Effectiveness (compare vaccinated with unvaccinated).
- Effectiveness shown for GW, and for CIN2+ in high coverage birth cohort.
- 2 doses 4+ months apart are as good as 3 doses in girls under 16.
- Older women (20+) need 3 doses.

Evidence-based general practice: prevention among healthy people (*John Brodersen*)

- Personalised benefit-risk balance?
- MMR – little harm, large benefits
- Pandemic influenza – little benefit, some great harm (narcolepsy).
- Scientific literature – benefits always reported, harms frequently not reported.
- Cytological screening, no randomised clinical trials (RCTs), meta-analysis on best available evidence, 56% reduction incidence, 35% reduction mortality.

Evidence-based general practice: prevention among healthy people (*John Brodersen*)

- RCTs for HPV vaccines:
  - Not all sexually naïve.
  - Not all 12 years old.
  - Contamination of controls – offered vaccine afterwards.
- Intention to be screened higher in vaccinated -> do not reach population at highest risk.
- Brochures information-poor and biased in favour of participation.

Evidence-based general practice: prevention among healthy people (*John Brodersen*)

- Do we need:
  - Higher quality in trials?
  - Another statistical significance level?
  - Adequate focus on potential unintended harms?

Danish Cancer Society (DCS) initiatives (*Ulla Axelsen)*

- 430,000 members, 45,000 volunteers.
- After 2013 -> communication plan.
- Facebook, fierce debate, negative reactions, discontinued.
- Post-factual society.
- Nevertheless, DCS still trusted by parents.
- Coordination and joint action with other stakeholders.

Danish Health Authority efforts to increase HPV vaccine uptake (*Bolette Søborg)*

- Public debate dominated by safety concerns.
- Danish cancer society and GP trustworthy, but also patient groups for girls who report Aes.
- Focus on those in doubt, +/- 33%.

Panel discussion

- Facts:
  - CaCx is caused by infection by hr-HPV, esp. 16, 18
  - Almost all high-grade precancers are caused by one of those hr-HPV
  - Vaccination of unexposed individual prevents infection, if not disease, see Australian data
  - Secondary intervention, no RCTs available, historical reasons
  - If you do not treat CIN3 with standard of care, 50% will progress to cancer (from unethical study in New Zealand)

Panel discussion

Questions:

- Q - Prior healthcare use, impression of the 700 patients? A - Both with and without previous experience in healthcare. Potential recall bias in health before problems.
- C - No epidemiological evidence to causally associate POTS with vaccine, common exposure 100,000s Danish girls receive vaccine, some have uncommon disease, no necessary association. Ill-defined diseases. Emotional appeal by anti-vax vs low-key response by pro-vax. Powerful and more rapid response needed, cacx patients on TV. A – Mothers asked for explanations, scientific response preferred over emotional response.

Panel discussion

- Q: Time-lapse between AE and vaccine? A: only 11 days between AE – vaccine. Only women with AEs within 2 months. Description of highly selected population, how to be treated, regardless of relation to HPV vaccine. Patients with unclear symptoms, not HPV vaccine Aes.
- C: Danish population is well-educated, wants to know, to participate. In Spain, when in doubt, people want to understand. Surveillance & monitoring, efforts to prevent side effects. Tools to detect AEs, narcolepsy was detected early due to monitoring. Causality requires a lot of data, takes time. Always dealing with biases. Not same incidence in different countries, how to explain? C: What about Australia? Excellent surveillance, not showing this signal. Or Scotland? Mothers seeing it happen to their daughter look for a cause, the vaccine is convenient. Need to provide evidence that it is not. C: Spain has lots of patients, who are not reported. In Japan, other name but same symptoms. Pre-implementation versus post-implementation.

Panel discussion

- C - Before vaccination POTS was also present, but now higher numbers. Diagnostic criteria unclear, lot of confounders.
- Q - Why is coverage in Denmark higher than in Norway, Sweden and Finland? A - Very successful catch-up program. Research will not solve whether there are safety issues with vaccine. Anti-vax semi-authorised by politicians and Association of disabled persons.

Panel discussion

- C - BR is investigated in phase IV trials, after licensure. On the risk side, auto-immune is a concern.
- C - Girls are sick and need treatment, that is first concern. Cause-effect relation should be investigated by serum study. Auto-antibodies detected provide a handle for treatment.
- C - Many small things worked together to crash HPV vaccine. 99.9% have no side effects. Those that do need to be heard, but a good vaccine should be used. Big RCTs, large phase IV, still signals possible.

Panel discussion

- C - UK – MMR story, somewhat similar. HCP should not be in war, bad signal to outsiders. Clear and united in messages, which are culturally appropriate. Clear about benefits of vaccine, and challenges of CaCx.
- C - Underestimated power of going out to the public collectively, how do we handle it from here? Social media can’t be ignored.
- C - Be humble in communication, acknowledge it is a big responsibility. Bring forward experience with FaceBook, sober, respectful.

Panel discussion

- Q - Are GPs trained to support the girls who have questions? A - The GPs in Aarhus feel not appropriately informed to support girls.
- C - Campaign launched with very emotional message. Wasn’t that too much? Initially successful, but may be more vulnerable, if suspicion comes up? Media more important.

Panel discussion

- C - Not just FaceBook, recognise YouTube as an important channel. A - Data show that decision is formed by the mother, not the girls themselves. The mothers are on Facebook.
- C - Irish experience, school-based program, strong anti-vax program, history very similar to Denmark. Politicians supportive of approach, HCP too. Same message from all HCPs, incl pharmacists, nurses, etc. Local media still opposed. How to convince general public? No direct access to media, but more quiet lately. Self-criticism among journalists after update on pre-vaccination healthcare seeking.

Panel discussion

- Q: Group selection in RCTs, what is the alternative? A - If not sponsored, no trials at all. Remain careful, also in other areas, not just vaccines. C: running RCTs costs lots of money, this can be spent wiser. A: RCTs were carefully performed, too expensive to be run by governments;

HPV Programs at a global level (*Ikechukwu Ogbuanu)*

- Only 67 countries (35%) introduced HPV vaccine.
- Not in highest risk countries, Africa/Asia.
- Global coverage below 15%.
- 60 M girls per birth cohort, >60% in 15 countries, of these only 4 have vaccine.
- Slow progression from GAVI demo projects to national introduction.
- Increase in coverage in most counties.
- Cost-effective delivery strategy for vaccination setting is essential, high coverage rate can be obtained with each setting.

HPV Programs at a global level (*Ikechukwu Ogbuanu)*

- Only 8 countries vaccinate men.
- WHO support for policy & decision making as well as planning and implementation is available.
- SAGE: reviewed effectiveness.

- Conclusion: Global uptake slow, reaching girls in low-risk countries.

What can we learn from HepB vaccine and other vaccine safety issues? (*Mark Kane)*

- Hepatitis B (hepB) vaccine introduced 1982.
- Vaccine prepared from blood product.
- aids discovered, virus still unknown, suggested in vaccine.
- Hiv not in vaccine, damage done to vaccine.
- DNA recombinant vaccine.
- Like HPV, HepB sexually transmitted virus.
- Initial recommendation: high-risk group.
- Failed to impact rates of disease.
- >90% countries use HepB vaccine universally, coverage 70-80%.

What we can learn from HepB vaccine and other vaccine safety issues? (*Mark Kane)*

- Safety concerns damage national programs.
- France: reported increase in Multiple Sclerosis in HepB vaccinated.
- Damage to French program still felt.
- Vietnam – program error led to drop from 76%- 56%, leading to 90,000 chronic infections and 17,000 deaths.
- Japan also quick to stop vaccination programs.
- In UK it took 12 years to recover confidence in MMR vaccine.

What we can learn from HepB vaccine and other vaccine safety issues? (*Mark Kane)*

- Spectrum of vaccine hesitance.
- Especially in alternative medicine.
- :Baxter paper 8 factors to oppose vaccination.
- Humans do not (always) make rational choices.
- Vaccine hesitance does not react to information.
- Role of the media.
- Rare condition – common exposure.
- Condition ill-defined.
- Claims damage programs before research can be done.

Discussion session 6

- Intro on state of vaccination.
- History of concern of side-effects of vax, and the consequences, role of alternative medicine in dodging vaccination.
- Problems in Denmark also have effects in other regions in the world, hesitation to introduce vaccine.
- Also effect on boys and men, not only CaCx. No longer indirectly protected, what can we learn from Austria.
- Gender neutral vaccination, more resilient to crises.

Discussion session 6

- In communities concerned about sex, gender-neutral vaccination solves the problem.
- In countries without screening vaccination is even more important, no fall-back mechanism.
- Put forward consequences of not vaccinating. Numbers for CaCx too low to impress. Pictures of CaCx? People need to understand the consequences.

Break-out group 1: definition success story

- Focus on HPV success.
- From which angle: public health (PH), individual?
- PH: High coverage, high impact, trust in vaccine in population.
- Better info to/training of GPs would have been helpful.
- Individual level: as long as it is good there is no need to discuss, no need to be aware of benefits.
- In crisis: how to recreate success? Anti-authority background – strong clear messages, more importantly: engage HCP network, independent, no conflict of interest, speak out in public, on social media.
- Bring down vaccination age to 9-10, to remove link to sex .

Break-out group 2: What can we learn for DK?

- Communication problem – not an issue of science.
- Media amplification.
- Speed in official/political response.
- Lack of training (HCP and media).
- Slow response to crisis.
- Involve media (owners/editors).
- Global leadership problem.
- One voice – unity.
- Don’t panic.
- Discuss positive sides, avoid negative campaigning.

Break-out group 2: What can we learn for DK?

- Rapid response team.
- Focal point needed to contact at WHO.
- Focus on gender-neutral vaccination, but plan carefully.
- Look at what works in other countries.

Break-out group 3: other countries with decreased coverage

- Analyse reason for drop in vaccination.
- React quickly.
- Have crisis plan with risk scenario.
- Leader / one voice.
- Include all involved, including teachers.
- Gender-neutral vaccination.
- Earlier start (age 9) to avoid psychogenic events.
- Evaluate benefits.
- Explain relation with industry, need to have new vaccines/drugs.
- Use WHO guidelines.

Break-out group 4: countries with satisfying coverage

- Programs are vulnerable.
- Complacency is a killer.
- Prepare for crisis.
- Learn from other countries as it spreads rapidly.
- Keep politicians supportive.
- Know the stakeholders, provide tailored info, to whom, how much and when.

Break-out group 4: countries with satisfying coverage

- Act quickly, but not rashly.
- Reach out to silent supporters.
- Understand population and opposition, issues around you.
- Train HCP beforehand, not after crisis -> challenge, proactively during MD curriculum, also for pharmacists.

Break-out group 5: role of the industry

Positives:

- Industry has data, expertise, early alert systems, can provide unrestricted grants for investigator-initiated research.

Risks:

- Involvement negatively perceived: commercially driven, too focused on product, not on immunisation.

Break-out group 5: role of the industry

- Where can industry help?
- Provide last, up-to-date information.
- Expertise in vaccines/immunisation programs worldwide.
- Experience with previous crises and errors.
- Support for networks of experts.
- Industry aligns communication with health authorities.
- Not naïve – transparency – share RCT data.
- More rules make it easier to operate.

Discussion

- Budget for buying vaccines, no budget for training and communication. Need for dedicated money, if only fraction of what is spent on the vaccines themselves.
- One voice – chorus of voices. Find ways to include advocates that match the very confident output from the anti-vax.
- One voice – expertise, but also personal qualities, feeling of trust, empathy. Different voices in different circumstances.
- Polio case – WHO immediately on top of it, measles the same. HPV: no response – no global leader for HPV. WHO organised 2 meetings, 2007, 2011.
- Monitoring – online, regularly updated. What does SSI do? Data for action, many interviews, reported to Danish Ministry of Health.

Discussion

- Everything started in Japan, in comparison Denmark and Ireland are doing relatively well. Nothing happens in Japan. Has effect world-wide, WHO should take firmer stand towards Japan.
- Program starts well before first shot, positive messages over negative messages, once launched stay prepared, have global outlook, need for training, one voice/leader/ambassador/champion, partnership with industry, pick right age for vaccination, may diminish some challenges.
- Need for clinics as safety nets for proper evaluation, to show that you give it attention. Take the problems seriously. Clinics may send double message: may be seen as recognition of association that has not been proven.