HUMAN PAPILLOMAVIRUS VACCINATION AND SCREENING IN THE ELIMINATION OF HPV-ASSOCIATED CANCERS:

EVIDENCE BASE FROM RANDOMIZED TRIALS

Matti Lehtinen

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Human Papillomavirus Vaccination and Screening in the Elimination of HPV-Associated Cancers: Evidence Base from Randomized Trials

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FOREWORD

In 2024, the world is on the brink of eliminating formerly common forms of human cancer, in particular cervical cancer. The story of how this happened contains many lessons to be learned on how a major public health improvement could eventually be accomplished. Professor emeritus Matti Lehtinen has with an incredible persistence pursued original research on this subject since the 1970s. An overarching theme has been that the adoption of new scientific concepts requires a maximally reliable evidence base. Already in the 1970:ies the Nobel Prize winner Harald Zur Hausen proposed that a new type of HPV could be the long-sought infectious cause of cervical cancer. After his discovery of the most important oncogenic HPV (HPV16) in 1983 and the completion of worldwide surveys and a large cohort study of HPV and cervical precancer in 1987, it would seem like the stage was set to eliminate the cancers caused by HPV. However, it would take some 4 decades of careful science to arrive at the goal.

A book by a researcher who has been actively working with this task ever since is a much-needed documentation of the key issues that must be addressed to achieve progress and also how to address them. The starting point is longitudinal cohort studies to establish etiology. This work had to start with first debunking earlier myths of herpes viruses as the cause of cervical cancer. Weak case-control studies had resulted in erroneous conclusion that kept being popular for many years until finally proven incorrect by prospective studies, a lesson on the need for strong study designs in etiological research that is worth contemplating for anyone interested in the correct etiology of diseases. HPV readily stood the test - prospective studies found it to be a strong risk factor for both cervical, anal, vulvar, vaginal, penile and oropharyngeal cancers.

The next phase was the evaluation of the safety and efficacy of HPV vaccines. When such trials were planned, there were important discussions regarding exactly what evidence would be needed. Repeatedly, there was a minority of only one person (Matti Lehtinen) who insisted on that the maximally reliable study design – randomized trials with invasive cancer as an endpoint - would be needed. As a result, such trials were performed only in Finland. With hindsight, it must be said that -although the final result of such trials took many years to complete - the fact that such studies were indeed performed and showed such strong cancer protection, is a very valuable basis for global elimination efforts.

The issue of which strategy to use for HPV vaccination is still being debated even to this day. Basic science and experiences from other vaccination programs clearly favored vaccination of both genders. However, the vaccination of only girls requires only half as many vaccine doses. Again, the assessment was that debates and predictions could probably continue for ever without reaching a clear consensus. Maximally reliable evidence from randomized trials of vaccination of girls only or vaccination of both genders would be required. Again, Finland is the only country that has provided the world with such evidence from the trials of Matti Lehtinen et al.

A stumbling block in many assessments of how to design a vaccination program is assessing the probability of type replacement. The concept means that if one virus type is eliminated by vaccination, some other type could appear. At one time, there was a plethora of uninformed studies on this subject. The concept described in the book is that this phenomenon could not possibly be seen before vaccine-targeted HPV types are near-eliminated in the population and that communities, where the vaccination strategy that achieves fastest HPV elimination (gender-neutral vaccination) has been used, would be the populations where the phenomenon

could best be quantified. As presented in the book, the phenomenon is indeed seen but has qualifications that suggest that it will not be of importance to public health.

The next issue to tackle was the need for cervical screening. The fact that cervical screening was introduced without any randomized trials as evidence base has hampered the development of optimal public health policies for many decades. In the future, if and when the necessary risk factor for cervical cancer (HPV) is missing, it is no longer meaningful to continue with cervical screening as before, particularly as the screening program is not devoid of side effects. The assessment here was that, as these screening programs have been performed for >60 years, policies and procedures were likely to be firmly entrenched and change would probably not occur unless maximally reliable evidence was provided by randomized trials. As far as I know, there are no other randomized trials of reducing screening in the world and the efforts that Matti Lehtinen describes are therefore both innovative and of obvious public health importance.

The final chapter deals with a very frequently asked question, namely "Once cervical cancer is eliminated, which other cancer form is next in line for elimination?". The obvious answer is HPV-associated oropharyngeal cancers that in Western countries are responsible for almost as many deaths as cervical cancers. During the times when HPV infection was common, HPV-based screening for oropharyngeal cancers was not realistic. However, in the era where HPV is nearly eliminated, the predictive values of HPV screening for oropharyngeal cancer will increase, and the development and evaluation of new screening modalities that could be used for the elimination of oropharyngeal cancer might result in that also this major form of human cancer becomes slated for elimination.

In summary, this comprehensive narrative on how an important evidence base for cervical cancer elimination was obtained is important to understand the development of a new concept for public health. The forward-looking chapters on how science could promote a switch from unnecessary over-screening for cervical cancer to a new screening program for oropharyngeal cancer puts forward a vision for the future that should be of interest to anyone interested in cancer.

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PREFACE

I have been involved with studies on the causes and control of cervical neoplasia for close to 45 years. Evidence that helps rejecting the non-causal association between herpes simplex virus type 2 (HSV-2) and cervical cancer [1-3], and confirms the association between previous infection with human papillomavirus type 16 (HPV16) and development of cervical cancer later in life [4, 5] emerged 30-40 years ago. Like other cancers, cervical cancer is a multi-etiological disease. In a number of our cohort studies it was possible to set order among independent pieces of the puzzle like smoking [6] and infection with *Chlamydia trachomati*s [7], or interacting pieces like non-oncogenic HPV types 6/11 [8, 9] and HLA-type [10]. Chapter I of this book ends with a suggestion: Data from our Nordic cohort study setting that successfully participated in dissolving the etiology of cervical cancer should now be used to evaluate the performance of artificial intelligence in causal inferencing up to change of paradigma. This is now timely also to understand and tackle the cervical cancer epidemic that has been ongoing among fertile-aged Finnish women over the last 25 years [11].

Prophylactic vaccination against a defined infectious cause of human cancer followed by elimination of the cancer is not only the ultimate proof of related causality, but also the most efficient means to alleviate, even abolish the given infection-associated cancer-burden. Proving hepatitis B-virus (HBV) vaccine efficacy against hepatocellular carcinoma took 25 years [12]. Our active, from the beginning population-based, participation to phase II to phase IV trials that involved HPV-vaccine development, licensure, and implementation of HPV vaccination have produced safety, immunogenicity and efficacy data for both the bivalent and quadrivalent vaccines (for a review see Lehtinen and Dillner [13]). Besides providing reliable and uniquely sensitive safety data our population-based approach with health-registry linkages provided long-term (up to 15 years) immunogenicity follow-up for a head-to-head comparison of the licensed HPV vaccines [14, 15]. First evidence on the efficacy of the HPV vaccine against human cancer was provided, this time in 10 years from the vaccine licensure [16] and also from the above-mentioned population-based setting as described in Chapter II.

The bivalent and quadrivalent HPV vaccines were the first highly efficacious vaccines licensed against sexually transmitted infections and their sequelae, including HPV-associated immediate precancerous lesions [17-21]. The implementation of these vaccines into national vaccination programs has, however, been a disappointment with global HPV vaccination coverage in the targeted female age-groups being 12%, and not more than 43% in high-income countries, where vaccine price should not be an issue [22]. It is obvious that the WHO campaign to eliminate cervical cancer by 2030 is bound to fail unless new scientifically sound approaches are soon implemented. Chapter III describes in detail the Finnish community-randomized trial on the impact of different HPV vaccination strategies. Comparing the gender-neutral and girls-only vaccination of early adolescent birth cohorts we have proven the superb effectiveness of gender-neutral vaccination in the introduction of herd effect against HPV types 16/18/31/33/35 in less than four years post-vaccination [23-25].

Following already moderate gender-neutral HPV vaccination coverage, the ecological niche of the vaccine HPV types 16/18 becomes essentially vacated in four to eight years [26]. Various epidemiological approaches to identify the replacement of the vaccine types with non-vaccine, high-risk HPV types either in vaccinated women [27, 28] or unvaccinated women [29-31] have been unequivocal to say the least. This may have been because of the extremely short follow-up time for a single non-vaccine HPV type to take over the vacated ecological niche [32]. However, an ecological approach managed to disclose abrupt changes in the overall HPV type-distribution and documented replacement of HPV-vaccine types in

the vacated ecological niche already four years post gender-neutral vaccination [26]. Chapter IV elaborates on how and why the ecological tools used were more suitable than conventional epidemiological tools when trying to disclose what was and is happening in the HPV population biology following prophylactic vaccination.

There is an imminent danger that the Swiss cheese model applies to preventative measures against cervical cancer. Females, who do not get vaccinated as adolescents are prone to be the least active participants in organized cervical cancer screening [33]. However, the HPV vaccination-derived herd effect extends protection also to the marginalized females. Besides the remaining high-risk HPV types identified in cervical lesions of the fully vaccinated sexually active population may have considerably lower progression potential [34, 35]. Chapter V elaborates on new possibilities in HPV-independent triage of cervical precancer in HPV-vaccinated women and women, who have been under herd protection and acquired cervical infections from non-vaccine HPV types only [35].

Non-cervical HPV-associated cancers comprise one of the last black boxes in terms of population-attributable fractions of vaccine HPV types. Especially, the rapidly increasing HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) calls for attention since it is already now as common as cervical cancer in a number of Western countries [36], and in the foreseeable future in a number of other countries as well. While prophylactic vaccination of HPV naïve birth cohorts is the ultimate solution also to HPV-associated OPSCC there are 30 to 50 young adult and middle-aged, most notably male birth cohorts that would benefit from effective screening of the disease. Most likely due to the anatomic location of the tumour, serological screening of HPV-OPSCC is possible due to the early appearance of HPV16 E6 protein antibodies 10 to 30 years before clinical diagnosis of the tumour. Chapter VI describes in detail the planned screening trial that again makes use of the Finnish cohort study setting with serum samples to be screened, which had already been taken 10 to 30 years ago [37].

In the post-vaccination era, when gender-neutral HPV vaccination has been implemented we are approaching the eradication of the most important oncogenic HPV types [11, 23]. This is qualitatively different from the WHO-pursued [38] elimination of cervical cancer below a certain low incidence (4/100.000) threshold. Finland is a striking example of how easily a country can slide above these arbitrary incidence thresholds. [11, 39]. How to reliably document impact and sustainability of such different public health interventions as prophylactic HPV vaccination, and screening and treatment of precancerous cervical lesions has not been solved yet [22]. On the contrary, the resilience of prophylactic HPV vaccination programs is being assessed as elaborated in the Endgame chapter.

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CHAPTER 1

Etiological Studies on Cervical Neoplasia – A Showcase of Causal Inferencing

Abstract: Preventive medicine is largely about identification of causes of diseases and their removal. Cervical cancer in Finland is firstly a showcase and secondly a use-case of preventive medicine. Firstly, etiological studies on cervical cancer were for long confounded by the fact that sexually transmitted infections are surrogates of both risk-taking behaviour in adolescent and young adult population, and occurrence of cervical cancer in middle-aged women. Identifying oncogenic human papillomaviruses (HPVs) as the true cause of cervical cancer among the multitude of different sexually transmitted micro-organisms required a Nobel-prize winning vision which was initially supported only by case-series evidence. It also required a paradigm shift that was facilitated by a correctly done epidemiological study and increased understanding on the molecular basis of exposure misclassification. All this was understood only after the etiological enigma had been resolved. Secondly, since the sexual revolution in 1960's first facilitated increase in risk-taking sexual behaviour associated sexually transmitted infections' incidence, and subsequently resulted in an increase in the incidence of cervical cancer. In the below Finnish use-case, the role of different causal (HPV16/18/31/45), intervening (*Chlamydia trachomatis*, smoking, HLA, HPV6/11) and non-causal (herpes simplex virus type 2) factors are put into perspective based on longitudinal, population-based studies. The established evidence base is now available for the evaluation of artificial intelligence/ machine learning performance in disclosing and judging causes of a chronic disease, cervical cancer.

Keywords: Artificial intelligence, Causality, Cervical cancer, Chlamydia, Evidence hierarchy, Herpes simple virus, HLA, Human papillomavirus, Nested case-control study, Smoking.

INTRODUCTION AND PREMISES

Medicine can be described as an observational science that is built in a very broad sense on medical disease history. In a philosophical sense causality in medicine, defined as a historical rather than physical science, is complicated (shown in the Conclusion of this chapter, and [40, 41]). However, judging what is truly causal in the context of chronic diseases, especially in the etiology of cancer, was pivotal for effective prevention already before the current rule of evidence based medicine in health care [42]. The recognition of cervical cytological changes

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(koilocytes) pathognomonic for the true etiological factors (human papillomaviruses) of cervical neoplasia [43] paved the way for successful implementation of a preventative measure, *i.e*., cervical Pap-screening [44]. With increased sensitivity and specificity stemming from the identification of the causal factor, the human papillomavirus (HPV) DNA cervical screening is still effective. In the following exercise, the difficulty and impact of assessing causal medical evidence hierarchy are evaluated in etiological and preventative research on cervical neoplasia.

I use this exercise to elaborate on the differences between conventional, scientifically verified causality as we know it in contemporary medicine compared to a newly coined term: causability in the context of artificial intelligence (AI) [45]. As a use-case to understand this dichotomy: causality *vs*.causability. I identify exposure trends to true causal factors of cervical cancer to human papillomavirus type 16 (HPV16) [5, 46] and smoking [6] *vs*. disclosure of non-causal associations with sexually transmitted infections such as herpes simplex virus (HSV) type 2 [1, 3, 5]. This etiological cervical cancer research was conducted as the Nordic serum bank and cancer registry collaboration that this author and professor Joakim Dillner coordinated, respectively between 1994-1999 and 2000-2009.

How to obtain and judge data on intervening factors: HLA (10), *Chlamydia trachomatis* [47, 48] and low-risk genital HPV types HPV6/11 (8, 9) is also pertinent. The exposure to the sexual risk-taking behaviour associated HPVs, most notably HPV types 6/11/18/31/33/45, and their interactions with or independence of the major cause HPV16, most notably in cervical carcinogenesis [49] is discussed. Finally, the impact of elimination and/or eradication of the true causal factors on the occurrence of cervical neoplasia incidence is contemplated from the causality *vs*.causability points of view with special reference to expected effectiveness of related public health interventions.

From the beginning of this exercise it is important to note that while AI-simulations on exposure associations, *i.e*., causability in medicine seem to exist at the personal level, understanding causality in medicine also exists at a system level [45]. Furthermore, the explanation types are as follows: Type 1) A peer-to-peer explanation as it is carried out, *e.g*. among physicians during medical reporting; Type 2) An educational explanation as it is carried out *e.g*. between teachers and students; and Type 3) A scientific explanation in the strict sense of science theory [40, 41] is at stake here.

Much of the etiological research on cervical neoplasia I have been involved with, and now reviewed as the use-case is associated with the last, Type 3 explanations.

On the other hand, AI-simulations seem to deal with the Type 1 explanation and need neither theory nor hypotheses. They are fundamentally different from conventional medical research, and difficult to catch.

By far medical research has strived to understand and control causes of diseases, using the above-mentioned Type 3 scientific explanations, and in the case of cervical neoplasia eventually with notable success (Chapters II, III and V). In the bigger picture, the issue is about how etiological research in medicine has been till now, and how it performs to provide data and deliver effective public health measures now and in the foreseeable future.

CHANGING SEXUAL RISK-TAKING BEHAVIOUR

In Finland, quadrupling numbers of life-time sexual partners have been evident over 40 years. This set the stage for the increase of cervical cancer incidence. A decrease in age at sexual debut and 50% increase in active smoking were both noted for 20 years between 1970 and 1990 but not later (Table **1**, [50 - 52]).

Table 1. Changes in surrogates of sexual risk-taking behavior and smoking in fertile-aged Finnish women between 18 to 45 years of age.

Year	Mean Number of Life-time Sexual Partners	Mean Age at Sexual Debut (%)	Proportion of Active Smokers (%)
1970	2.5	18.9	16
1990	6.9	17.1	26
2000	7.9	16.6	20
2010	9.9	16.6	15

Haavio-Mannila *et al*. 2001, Kontula *et al*. 2008, THL Reports, Kouluterveyskysely 2022.

Since late 1990`s, for more than 25 years the incidence of invasive cervical cancer has been continuously increasing from less than 4 per 100,000 to 16 per 100,000 person years in fertile-aged women (Fig. **1**), [11]. The rigidness of the initially successful organized cervical screening which for 50 years has always got started at age 30 with 5-year intervals in the face of rapidly increasing risk-taking behaviour has proven a showcase on what can happen when disease prevention is not apt to contain changes of risk-taking behaviour and the associated increase of carcinogenic exposure.

Decrease of age at sexual debut plateaued and smoking returned to the levels seen in 1970`s almost 20 years ago, yet the incidence of cervical cancer keeps on increasing. Trying to understand exposures that caused and are still causing the epidemic of cervical neoplasia in fertile-aged Finnish females, we can start by

CHAPTER 2

Safety, Immunogenicity and Efficacy of Human Papillomavirus Vaccines

Abstract: Seizing the day is pivotal in vaccination licensure studies, especially when the new vaccine is supposed to protect against a chronic infection with long lead time between the preventable infection and diagnosis of the to-be prevented chronic disease. With appropriate population-based design, that relied on the unique Finnish personal identification number comprehensive health register follow-up was feasible for the definition of safety, immunogenicity and efficacy of both the bivalent and quadrivalent human papillomavirus (HPV) vaccines soon after their licensure. In essentially HPV vaccination naïve population head-to-head comparison of the two vaccines was also feasible. Respectively, in 2002 and 2004 enrolled 1,749 and 4,809 adolescent girls around the ages of 16-17 years were respectively participated in two phase III licensure trials (FUTURE II and PATRICIA) of the quadrivalent and bivalent HPV vaccines. At the same time in 2003 and 2005, 15,615 adolescent, 18-19 year old girls from adjacent birth cohorts were enrolled into a concomitant control cohort. Linkage of the HPV vaccinees cohort with the population-based Finnish Maternity Cohort Serum Bank enabled comparative head-to-head studies on the quadrivalent and bivalent vaccine-induced total and neutralizing antibody responses, which were proven to be equally sustainable up to 12 years post-vaccination, however, with a logarithmic difference in the antibody levels. Linkage of the HPV vaccinees cohort and the concomitant control cohorts with the country-wide Finnish Cancer Registry has enabled the definition of vaccine efficacy (VE) against invasive cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3+) during 18 years of follow-up with comparable intention-to-treat VEs of 68.4% and 64.5%. Linkage with the Hostital Discharge Registry has provided a sentinel, most notably for new onset autoimmune diseases (NOADs) that proved to be more than twice as sensitive as reporting of serious adverse effects but as such did not identify any NOAD-incidence differences between the HPV and control vaccines or unvaccinated population.

Keywords: Efficacy, End-point, Enrolment, Follow-up, Health registry, Immunogenicity, Population-based study, Randomization, Safety, Vaccine efficacy.

INTRODUCTION AND PREMISES

The prophylactic vaccination involves healthy individuals who would not need the specific vaccine shots without exposure to the respective micro-organism.

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Since such exposure and the following infectious disease, even in its epidemic phase, not always materialize in all vaccinated individuals, the adverse effects from prophylactic vaccination must be milder than those of catching the disease. Both the vector used to present the vaccine antigen and adjuvant used to augment the vaccine-induced immune response have not infrequently caused more severe adverse events: embolism following coronavirus vaccination with the adenovirus vector-derived vaccine [86]. and narcolepsy following influenza virus vaccination [87] compared to the prevented diseases would have been caused in adolescent and young adult women or children, respectively. Regrettably, both of the above-mentioned examples have also shown that vaccine manufacturers tend to belittle or deny unexpected adverse effects that emerge after mass vaccination. At the end of the day, it is the responsibility of public health authorities when launching national vaccination programs to provide adequate sentinels and/or surveillance systems for newly licensed vaccines like the more or less effectively adjuvanted HPV vaccines (see below).

Long-term vaccine-induced immunity, most notably sustainability of protective neutralizing antibody levels for decades is pivotal when exposure to the targeted micro-organisms is present continuously (*e.g.*. *Clostridium tetani*) or for decades (oncogenic human papillomaviruses). In the former case, of the tetanus toxoid vaccine, bolstering the initially induced protective immunity has become routine. This means the provision of additional shots of the single protein tetanus toxoid vaccine *e.g.*. with up to 20-year intervals. The widely used hepatitis B-virus (HBV) and HPV vaccines are also comprised of a single protein which, however, assemble into empty virus-like particles (VLPs), and with repetitive epitopes are better immunogens than the above-mentioned toxoids [88]. Not infrequently, however, due to genetic factors (HLA-DR4) it takes several additional vaccine shots to generate HBV antibody levels that confer protective and sustainable immune response [89]. As noted above, the VLP vaccines can be more or less adjuvanted with a dramatic (logarithmic scale) effect on thereby induced antibody levels [15, 90].

On the other hand, adding progressively more virus types into the multivalent vaccines tends to decrease the overall vaccine immunogenicity. In the case of quadrivalent HPV6/11/16/18 VLP-based HPV immunization, HPV18 antibodies are neither generated at all in up to 15% of vaccine recipients [91] or virtually lost in less than five years [92], and in the case of both the quadri- and nonavalent vaccines significantly lower than those induced by the bivalent vaccine [90, 93].

The late Maurice Hilleman noted at the 1st Helsinki HPV workshop in 2000 that there is no sterilizing immunity [94]. In addition, to be efficacious, the reduction of the infectious human papillomavirus dose by HPV-vaccination needs to

provide both the immunity against manifest infection and the long-term protection against HPV-related cancer [13, 16], most notably cervical cancer. Since cervical cancer probably originates from a single infected and consequently malignantly transformed cell, the success of reducing viral load, *i.e*., the number of infected cells below the plausible threshold of neoplastic development [95] is pivotal here.

In 2001, when preparing for phase III licensure trial of what is now known as the quadrivalent HPV6/11/16/18 vaccine Merck vice-president Ed Skolnick remarked that there is no ethically sound way of providing data on the efficacy of a human vaccine against a cancerous end-point directly from randomized clinical trials. In the end of this chapter, I will discuss how this data was anyhow generated from our overlapping cluster and individually randomized trial setting [96, 97] in young adult women exploiting population-based recruitment of adolescent females and country-wide cancer register.

SAFETY OF HUMAN PAPILLOMAVIRUS VACCINES

Instead of opportunistic vaccination with the newly licensed bivalent and quadrivalent HPV vaccines, Finland in 2007 launched a population-based, community-randomized phase IV trial on the effectiveness of different HPV vaccination strategies [97], refer to Chapter IV Impact of human papillomavirus vaccination strategies. Aside from the effectiveness /impact end-point, end-points of this phase IV trial were safety end-points based on country-wide post-vaccination health-registry surveillance.

The trial participants were minors, 12 to 15-year-old girls and boys from 33 out of 34 Finnish communities (outside the Helsinki Metropolitan regions) with at least 35,000 inhabitants. The informed consents, even after providing the invitees with 10 pages of information on possible side-effects, were obtained from vaccinees and, in general, their highly vaccination-prone parents. These yielded permission to use the participant's personal identifier for post-vaccination health registry linkages. Approximately 52% of (20,514 of 39,420) girls and 20% to 30% of (11,662 of 40,852) boys participated equally well into the community-randomized trial, except for three communities. Lower than the a priori set cut-off level for low participation (20% relative difference from the mean coverage [24] was noted in one Arm B and, two Arm A communities on the western coast of Finland, of which one is notorious for anti-vaccinology attitudes.

Linking the PI-maintained Registry of Vaccinees with the Finnish National Hospital Discharge Registry for new onset autoimmune diseases (NOADs, Appendix) up to age 18.5 years took place after completing vaccination by the end of 2010 (interim analysis) and at the end of the trial in 2014 [98, 99]. In general, no abnormal safety signals were noted in the health registry follow-up.

CHAPTER 3

Impact of Different Human Papillomavirus Vaccination Strategies

Abstract: The overall impact of vaccinating a population, *i.e*., overall effectiveness always comprises direct effectiveness (vaccine efficacy) and indirect effectiveness (herd effect) of vaccination. In the case of human papillomavirus (HPV) vaccination the role of herd effect is especially strong due to the assortative nature of sexual risk-taking behaviour and transmission of sexually transmitted micro-organisms, including genital HPV types. At the time of HPV vaccine licensure we launched a community-randomized trial in Finland to provide real-life evidence on the impact of different vaccination strategies one of which was to be implemented into national Finnish vaccination program. In collaboration with the Finnish National Institute for Health and Welfare we invited in Autumn 2007 all 80,272 boys and girls from 1992-1995 birth cohorts, who attended one of the 250 junior high-schools in overall 33 Finnish towns outside the Helsinki Metropolitan regions. The study sites represented 33 of 34 Finnish communities with >35,000 inhabitants and were randomized 1:1:1 into 11 gender-neutral HPV-vaccination communities, 11 girls-only HPV-vaccination communities, and 11 control (hepatitis B-virus) vaccination communities. Furthermore, with both parental and their own informed consent 20,513 girls and 11,662 boys participated in the school years 2007-2009. Between 2010 and 2014 11,396 cervical samples for HPV typing were obtained from 18.5 year-old females. We identified superb herd effect in the gender-neutral HPV vaccination communities against transient HPV18/31/33/35 infection as defined by PCR positivity and against persistent HPV type 16/18/31/35 positivity as defined by serology. Statistically significant rapid elimination of HPV types 18/31/33 by birth cohort was found only in the gender-neutral HPV vaccination communities. This study was possible only in the HPV vaccination naïve population, and the findings supported the implementation of gender-neutral HPV vaccination two years after their publication.

Keywords: Core group, Cumulative incidence, Effectiveness, Herd effect, Prevalence, Sero-prevalence, Vaccination coverage, Vaccine efficacy.

INTRODUCTION AND PREMISES

Establishing herd effect against sexually transmitted human papillomaviruses in the general population is, not surprisingly, prone to be efficient due to the assortative nature of risk-taking sexual behaviour [116]. In plain words, this is due to the fact that partners of individuals with low number of sexual partners also

have low number of sexual partners – this has been and in many countries still is an essential characteristic of the general population. With up to 70% of the entire population acquiring at least one sexually transmitted HPV infection during lifetime it is the general population that matters here. In this context, it is noteworthy that genital HPV infections do not cluster with venereal infections like syphilis, gonorrhoeae, chlamydia or genital herpes which are surrogates of sexual risk-taking behaviour [117].

The first mathematical models on the overall effectiveness of HPV vaccination considered both direct vaccine efficacy (direct effectiveness) and herd effect (indirect effectiveness). The models that exploited population-based Finnish input data on sexual behaviour and occurrence of genital HPV infections predicted with low (30%) to moderate (70%) vaccination coverage statistically significant differences between the overall effectiveness of gender-neutral *vs*.girls-only vaccination strategies [118 - 120].

Knowing that passive Finnish Cancer Registry follow-up of our cluster (birth cohort) and individually randomized phase III trials were bound to deliver sound estimates on HPV-vaccine efficacy against cancer in 10 to 15 years [16, 96, 121]. I started to contemplate how to evaluate the effectiveness of different vaccination strategies in real life. Learning about the community-randomized trial setting in evaluating the effectiveness of different HIV interventions from King Holmes at the 1st Helsinki HPV Symposium in 2000 was seminal [116], and drafting comparison of the different HPV vaccination strategies in a community-randomized trial got started [119, 122].

For the funding of the desired effectiveness of different HPV vaccination strategies our contributions in the phase III HPV vaccination trials were very important. Most notably reaching the interim event-driven efficacy end-point fit for vaccine licensure [18] due to extra recruitment of 1500 Finnish adolescents in just a few months in early 2005 was pivotal.

At the time both GSK Biological and Sanofi-Pasteur-MSD (then the Europe distributor of Merck`s quadrivalent HPV6/11/16/18 vaccine) were both interested in the services of our sound country-wide vaccination trial infrastructure. Negotiations with Sanofi-Pasteur MSD about the phase IV trial ended in late Autumn 2006 when Sanofi-Pasteur deemed the anticipated trial too expensive for the mere support of European delivery of the quadrivalent vaccine. However, in early 2007 I managed to sell the protocol (and study setting) of the below-described phase IV trial to GSK Biologicals for randomized implementation of their newly licensed bivalent HPV16/18 vaccine in Finland. For GSK the trial was partially to generate population-based safety data for the newly licensed vaccine

but highly likely also to gain a foothold for HPV vaccination programs in northern European countries. Anyways, without GSK Biologicals` funding this unique phase IV trial on the overall effectiveness of HPV vaccination strategies, not mere direct HPV vaccine effectiveness (vaccine efficacy, sic) conducted between October 2007 and December 2014 would never have materialized.

The premises of this chapter were to elaborate the effectiveness of different HPV vaccination strategies implemented/assessed in Finland as a country-wide community-randomized phase IV trial [24, 31, 97, 123, 124]. The co-primary trial objectives, which I collaboratively designed and finalized with Gary Dubin (GSK Biologicals) and Geoff Garnett (Imperial College London) were to assess total effectiveness comprising direct effectiveness (vaccine efficacy), and indirect effectiveness (herd effect) of HPV vaccination in the gender-neutral arm or in the girls-only arm as compared to the control arm [97, 119]. The secondary objectives were to test the indirect and direct effectiveness of vaccination in HPV-vaccinated and control arms, *via* statistically powered comparison of the HPV-vaccinated gender-neutral arm *vs*.control arm and HPV-vaccinated girls-only arm *vs*.control arm.

This phase IV trial was launched immediately after the licensure of the bivalent HPV16/18 vaccine in October 2007 [97] the target population being early adolescent girls and boys of entire birth cohorts from 1992-1995 in 33 of 34 Finnish towns outside the Helsinki Metropolitan area with a minimum distance of 50 kilometers to avoid undue mixing of the adolescent population. Finally, in 2020 Finland launched gender-neutral HPV vaccination basing partially on our randomized trial data of the superb herd effect and total effectiveness of gender-neutral HPV vaccination as compared to girls-only HPV vaccination [24, 25, 97, 123, 124] (Fig. **9**).

HERD EFFECTS GENERATED BY GENDER-NEUTRAL AND GIRLS-ONLY HPV VACCINATION

The most important prerequisite for estimating vaccination (program) generated herd effect, especially the effectiveness of different vaccination strategies in the herd effect generation is to have a vaccination-naïve target population willing to participate a randomized trial. When the licensure of the quadrivalent and bivalent vaccines to 15+ year-old females in the EU (Finland included) took place during Autumn 2006 and 2007, their very high price and slow opportunistic purchase kept the general Finnish population secluded from mass vaccination. This created an optimal vaccine naïve population to launch our community-randomized trial in October 2007. Overall, less than 1,000 full, three-dose regimen were sold to adolescent and young adult females in Finland before onset of our phase IV trial,

CHAPTER 4

Vaccination and Human Papillomavirus Type-replacement

Abstract: We anticipated that moderate human papillomavirus (HPV) vaccination in the Finnish community-randomized trial will demonstrate changes in ecological niche of the circulating HPVs such as the niche occupation by non-vaccine-covered HPV types. In this study we exploited a re-randomized cervical screening trial that had been launched in 2014 among 14,686 HPV-vaccinees starting from 22-year-old omen, born in 1992 (refer to Chapter V). Approximately half of the HPV-vaccinees, 6,958 women participated the trial and provided serial cervical samples for HPV typing at ages 22, 25 and 28 years. With the trial follow-up we could verify the more (gender-neutral vaccination arm) or less (girls-only vaccination arm) efficient vacation of ecological niche initially occupied by the vaccine-covered HPV types 16/18/31/45 up to eight years post-vaccination. However, no consistent changes were observed neither in the gender-neutral arm nor in the girls-only arm in epidemiological analyses for the non-vaccine-covered HPV39/51/52/56/58/59/66/68/73 determined by PCR of cervical samples or by serology. In contrast, our analyses at the community level revealed rising ecological diversity of the more or less non-vaccine-covered HPV types 33/35/51/52/56/58/59 in gender-neutral vaccination communities with a stronger herd immunity compared with girls-only vaccination communities from four to eight years post vaccination. This is probably the first recorded sign of niche occupation by the non-vaccine-targeted HPV types post-population level vaccination.

Keywords: Alpha-diversity, beta-diversity, ecology, human papillomavirus, prevalence, seroprevalence, Shannon-index, type-distribution.

INTRODUCTION AND PREMISES

Prophylactic vaccination against micro-organisms is probably the most powerful imaginable public health intervention in human population biology. Most notably it can be highly cost-effective with sustainable impact, for example, eradication of small pox 50 years ago is still annually saving 70 million dollars [131]. However, there are caveats following vaccination, for instance replacement of vaccine-covered microbial types has been recognized world-wide since the ground-breaking work of Dr. Marc Lipsitch. Using a mathematical model he predicted more than 25 years ago how vacation of an ecological niche following vaccination would result in a replacement of the vaccine-covered bacteria by the non-vaccine

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-covered bacterial lineages of the same micro-organism [132]. During the following decades worldwide, when pneumococcal vaccination programs were implemented a replacement of the vaccine-covered pneumococci types by non-vaccine-covered pneumococci was observed [133]. Unfortunately some of the replacing pneumococcal types, most notably *S. pneumoniae* type 19A, have been methicillin resistant [134].

Changes in microbial species subtype distribution also happen without vaccination, for example following migration. This became evident when *C. trachomatis* serotypes common in Finland during the 1980`s were abruptly, replaced during the 1990's by other *C. trachomatis* serotypes following free, rapidly increasing traffic over the Finnish – Russian border after the breakdown of Soviet Union in 1991 [135]. Twenty years later, when the border-traffic had been normalized the *C. trachomatis* serotypes returned back to those characteristics in the Finnish population before the opening of the border. Thus, rapid changes in the subtype-distribution of sexually transmitted (intracellular) micro-organisms can also take place following population mixing and the establishment of new transmission networks.

The notable mixing of the vaccinated and unvaccinated population happens following the implementation of HPV-vaccination programs, especially the school-based programs. Within a few school years immunity and/or protection against most common HPV types are spread following direct and indirect (herd) effects of vaccination in the entire adolescent population. At the early stages of HPV vaccination campaigns the protected adolescent population mix with unvaccinated young adults among whom genital HPV types are extremely common with a prevalence of over 30% [54, 123]. This set-up for HPV type-replacement has been established in all Western countries that are implementing HPV vaccination programs.

Furthemore, I will elaborate on how we have studied with epidemiological, mathematical modelling and ecological means vaccination-induced changes in the population biology of HPV types exploiting our community-randomized trial setting. The comparison of originally HPV-vaccination naïve communities within which gender-neutral HPV vaccination, girls-only HPV-vaccination or HBV vaccination was implemented to four (1992, 1993, 1994, 1995) birth cohorts during two school years from 2007 - 2009 has given us a unique possibility to study HPV-vaccination related type-replacement. In addition, providing new data it has also been a learning experience to the limitations and gains of the three above-mentioned disciplines [26, 29 - 32].

EPIDEMIOLOGICAL APPROACHES TO HPV-VACCINATION AND ASSOCIATED TYPE-REPLACEMENT

Relying on vaccination-prone population and well-trained study personnel, who had successfully completed large-scale phase III and phase IV HPV vaccination trials all over Finland, we acquired population-based data for HPV type-replacement studies. This has required more than 15 years of hard work in conducting the community-randomized phase IV implementation trial between 2007 and 2014, and ensuring its follow-up as an individually randomized screening trial from 2014 onwards up to 2024 [11, 23]. In the previous Chapter III, I described how this database has been used in studies comparing the impact of different HPV vaccination strategies on occurrence of vaccine-targeted HPV types. The added value of these studies, studies on type-replacement following HPV-vaccination is described below.

In the first place, we reached out for the epidemiology tool box. We had successfully used the comparison of overtime changes in the relative proportions of microbial subtypes to disclose migration-related *C. trachomatis* type-replacement in the 1990's [135]. Thus, we first tested if the ranked order of non-vaccine covered genital HPV types' (HPV6/11/39/51/52/56/58/59/66) prevalence as determined by cervical PCR positivity would change differentially in the gender-neutral vaccination communities as compared to the girls-only vaccination communities, or in the control vaccine communities [29, 30]. No changes in the relative proportions of genital HPV types that could have been specific for a specific mode of the above-mentioned interventions were observed. Until age 22, *i.e*., approximately 8 years post-vaccination the ranked order of genital HPV types among the non-vaccine-covered HPV types remained essentially the same in all consecutive birth cohorts (1992-1995) participating the community-randomized trial [30, 31].

Next, we evaluated epidemiological differences in type-specific HPV prevalence by arm. We used the community-randomized trial setting to compare arm-wise (gender-neutral *vs*.control arm, and girls-only *vs*.control arm) PCR prevalence ratios (PR) of HPV types 6/11/16/18/ 31/33/35/39/45/51/52/56/58/59/66/68 in cervical samples taken from vaccinated or unvaccinated women aged 18 and 22 [29, 30]. On the other hand, we compared pre- and post-vaccination trial seroprevalence (*i.e*. cumulative incidence) ratios (SPR) of HPV types 6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/68/73 in the gender-neutral arm, in the girls-only arm and in the control arm among 22-year-old and younger unvaccinated women [31]. In addition to the general female population, we assessed the PR and SPR estimates in sexual risk-taking behaviour core groups,

CHAPTER 5

Screening and Triage of Cervical Neoplasia in HPV-vaccinated Women

Abstract: We have been running an individually randomized cervical screening trial since 2014. All 14,686 HPV-vaccinated women from birth cohorts 1992-1995, who had received three vaccine shots between 12 to 15 years of age (12,402) or at 18 years of age (2,284). They were invited to participate in an individually randomized trial on infrequent *vs*.frequent cervical screening visits at ages 22, 25 and 28. The infrequently screened arm participants are informed only on cytological findings indicative of colposcopy and conisation, *i.e*., high- grade squamous cervical intraepithelial lesion (HSIL) or adenocarcinoma *in situ* (AIS). Furthermore, due to in-country migration female residents in one of the original 33 vaccination trial communities or after having moved to the Helsinki Metropolitan Region after 2014 were eligible. Altogether 6,958 women consented with a very high (over 92%) compliance to participate in the second (6,381 women) and the third (4,616 of 5,100 women vaccinated as early adolescents in 2007-2009) screening visits. The occurrence of cervical lesions: ASCUS, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and adenocarcinoma *in situ* has been equal in the different arms. The progression potential of the HSIL findings in the HPV16/18 vaccinated women is probably reduced as suggested by the identification of hypermethylation of HPV-independent cervical cancer risk genes in only a few of the diagnosed HSIL cases. A randomized trial to compare mere clinical follow-up *vs*.treatment of HSILs diagnosed in vaccinated women is highly warranted.

Keywords: Cervical cancer, Epigenomics, Human papillomavirus, High-grade squamous intraepithelial lesion, Methylation, Screening.

INTRODUCTION AND PREMISES

Following World War II, sexually transmitted infections, most notably syphilis and gonorrhea were common in many Western countries, including Finland. In Finland, and many other European countries the birth rate and the incidence of subtle cervical infections with oncogenic human papillomaviruses most likely peaked during the late 1940`s and early 1950`s. Following an approximately 15 to 20 years lead time the latter resulted in cervical cancer being the most common cancer in Finnish females during the 1960`s and 1970`s.

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Population-based Pap-screening of women between the ages 30 and 60 years was launched in 1963 in Finland to tackle the situation. Fortunately, the timing of this intervention was an important factor in the very successful outcome: rapid reduction of cervical cancer incidence below the WHO-recommended 4/100.000 by the beginning of the 1990`s [44, 78].

The data on the underlying incidence of the then unknown genital oncogenic HPV16/18 infections, which was not known during 1960`s does not exist. However, deducing from the relatively low levels of sexual risk-taking behaviour still in the early 1970`s (Table **1**, [50]) HPV16/18 (and other oncogenic HPV) incidence may have been at its (post-World War II) lowest among adolescent and young adult women in the 1960`s, just before the two successful decades of organized cervical screening in Finland from 1970 to 1990.

Chapter I reviews population-based studies on the dynamics of HPV6/11/16/18/31/33 epidemics as indicated by seroprevalence (cumulative incidence) during 1980`s and 1990`s. There is scarce data from the Finnish Mobile Clinic Health Survey serum bank that HPV16 seroprevalence was very low at the beginning of 1970`s. However, the sexual revolution swept through the adolescent and young adult Finnish population, both female and male, in the 1970`s and continued through the 1980`s and the 1990's. Consequently, from the 1980`s to early 1990`s especially the cumulative HPV16 infection incidence more than doubled in young adult Finnish females (Fig. **5**, [54]) which was followed by continuously increasing incidence of invasive cervical cancer in fertile-aged females since the early 1990's (Fig. **6** [10, 11]).

With the risk-taking sexual behaviour spreading (in terms of high numbers of sexual partners) throughout the entire fertile-aged population [51] the HPV16 epidemic reached a plateau not earlier than by the middle of 2000`s [57, 83]. Moreover, the rising cervical cancer incidence in the fertile-aged Finnish women [11] indicates the inability of organized cervical screening to tackle the adverse effects of subsequent HPV16 infection and cervical cancer epidemics, the two being the first and the second, but probably not the last population level sequelae of sexual revolution. How to tackle related imminent epidemic of oropharyngeal cancer in 60+ year-old men and women is elaborated in Chapter VI of this book.

On the flip side of inadequate cervical screening are its adverse effects, namely the increased risk of preterm birth (PTB) and PTB-associated fetal mortality [101]. However, even under such severe adverse effects with thousands of fetal deaths discovered over the 70 years of organized screening in Sweden (Dillner J, personal communication) and Finland – no major criticism has been raised. However, with the HPV-vaccination program induced rapid reduction of true

causes of cervical cancer, most notably HPV vaccine or vaccine-covered types 16/18/31/45, the positive predictive value of any cervical screening (HPV and cytological screening alike) is lost [136]. This will result in the vast majority of future positive findings in cervical screening being false positive findings. This is true regardless of which HPV-dependent screening method is used. Largely HPV-independent screening modalities, most notably the identification of hyper-methylated cellular cervical cancer risk genes has lately raised plenty of attention in this respect [34].

Identification, diagnosis and treatment of precancerous cervical lesions, which ever more often do not have progression potential, is now a common adverse effect of this previously beneficial public health intervention. Among the fertile-aged Finnish women, organized cervical screening devoid of any beneficial public health impact [11] has been ongoing for the last 25 years. On the contrary, there is good, albeit indirect evidence that avoiding the identification, diagnosis and treatment of precancerous cervical lesions in HPV-vaccinated women is significantly reducing their preterm birth rates [102]. In the forthcoming years our intention is to test in a randomized trial whether follow-up rather than treatment of precancerous (HSIL/AIS) cervical lesions caused by non-vaccine HPV types in HPV-vaccinated women is the optimal choice. In the foreseeable future, deviating from HPV science-based new standard of care towards unnecessary conisation may turn out to be a criminal offence against the health of an HPV-vaccinated woman.

SAFETY OF INFREQUENT CERVICAL SCREENING OF HPV-VACCINATED WOMEN

In 2014, we launched an individually randomized trial on the safety, accuracy and impact of infrequent *vs*.frequent cervical screening in women, who had received HPV16/18 vaccination in 2007-2009 as early adolescents between ages 12 to 15 years, *i.e*., before exposure to oncogenic HPV types [138]. Our trial involves three screening visits at ages 22, 25 and 28 with the infrequent screening arm blinded on cytological cervical findings milder than high-grade squamous cervical intraepithelial lesions (HSIL) or cervical adenocarcinoma *in situ* (AIS) as compared to frequent screening arm where all cytological findings obtained at each visit are openly delivered to the trial participants. According to the local standard of care cytological HSIL/AIS lesions are indicative of colposcopy-directed biopsy followed by possible conisation.

The trial is conducted in the HPV-vaccination communities that took part in our community-randomized phase IV trial on the impact of different HPV vaccination strategies from 2007 to 2014 (see Chapter III). However, due to in-country

CHAPTER 6

Screening of Human Papillomavirus Related Oropharyngeal Cancers

Abstract: During the last 30 years the incidence of head and neck cancers associated with human papillomavirus type 16 (HPV16) has rapidly increased in Finland and is now three-fold higher compared to 1990's also in neighbouring Scandinavian countries, most notably Sweden. This is due to the widespread increase of HPV16 infection that started in the 1980's both in Finland and Sweden. While, the recently launched, school-based gender-neutral HPV vaccination will eventually eliminate HPV-associated head and neck cancers preventing up to 1,000 annual cases in the Nordic countries, there are at least 30 birth cohorts that urgently need screening and treatment of the HPV-associated head and neck cancers. This chapter first evaluates the prospects of the elimination of HPV-associated head and neck cancers by gender-neutral HPV-vaccination. Thereafter a proof-of-concept screening study that exploits the population-based FMC Serum Bank comprising first-trimester blood samples which were collected for serological screening from virtually all, 96% of the one million Finnish women, who were pregnant between 1983 and 2016 is characterized.

Keywords: Early antigen, Head and neck cancer, Human papillomavirus, Screening, Serology, Tongue cancer, Tonsillar cancer.

INTRODUCTION AND PREMISES

Plausible eradication of oncogenic HPV types, the necessary cause of cervical cancer [80], has opened the door for the elimination of most HPV-associated cancers. In fact, elimination of oropharyngeal HPV-associated cancers might be easier than the cervical cancer elimination because of a number of reasons: Cervical cancer is linked with a number of oncogenic HPV types: most notably with types 16/18/31/33 in squamous cell carcinomas and types 16/18/45 in cervical adenocarcinomas [48, 156], while most (>90%) HPV-associated head and neck cancers are positive for HPV16 alone [157].

The increasing incidence of head and neck cancers in Western countries (most notably the US and Nordic countries) has become evident 20 to 30 years following the start of HPV16 epidemics in these countries [54, 157 - 160]. In the western countries the incidence of head and neck cancers has increased in the last 30 years particularly in males. The increase is partially due to changes in sexual

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behaviour and the associated increase of HPV16 infection, readily acquired due to its high reproductive rate and persistence [54, 118, 161]. The increase was first observed as increasing incidence of tonsillar and base of tongue cancers in Swedish males [160]. Over the last 30 years similar three to four -fold increases in the overall incidence of head and neck cancers, particularly in oropharyngeal cancer (OPC) have been registered in all the four Nordic countries [162].

One of the highest increases in age-specific OPC incidence has been documented in 50-69- year-old Nordic males among whom the annual occurrence has increased from 150 up to 500 cases. This increase was preceded by the epidemic increase of HPV16 infection incidence in the fertile-aged population during the 1980s and 1990's in Finland and the other Nordic countries [54, 160, 161]. On the other hand, the long lead time from persistent HPV16 infection to OPC has only gradually revealed these changes, and the incidence increase is now becoming more and more striking with an increased pace decades after the start of the HPV16 epidemics. Notably also the incidence of familial OPC in spouses of women with anogenital neoplasia increased up to 5-fold between 2000 and 2015 (Fig. **12**) [163]. Familial HPV-cancers probably add up to the rapidly increasing incidence of HPV-associated OPC incidence in all Western countries. Furthermore, an increase of the OPC incidence in 70-85+ year-old females has recently been noted in the Helsinki Metropolitan area [162]. This also fits with the HPV16 epidemic starting in the 1980's in Finland and with the longer lead time between the incidence peaks of HPV16 infection and OPC (approximately 45 years) than that between HPV16 infection and cervical cancer (approximately 15 years).

Eventually, the implementation of gender-neutral HPV-vaccination programs that are predicted to eradicate HPV16 with a moderate 75% vaccination coverage [11, 23] will result in the elimination of also HPV-associated head and neck cancers. However, the notorious persistence of acquired HPV16 infections will continue to cause increasing numbers of OPCs for the next decades. Thus, an effective secondary prevention, *i.e*., the screening of HPV-associated OPC is needed to protect the middle-aged birth cohorts that can no longer benefit from prophylactic HPV vaccination. Even if oncogenic HPV infections are a necessary cause of all cervical cancers [80] it is involved in less than 70% of OPCs [36]. For instance, regarding oral cavity cancers only 3% are HPV positive. This, makes it increasingly important to further investigate what kind of OPC types should be screened for and how?

In addition to highly effective HPV vaccination, both HPV-serology [164 - 168] and HPV DNA-detection [36] -based screening of HPV-associated OPCs exist. Possibilities for the elimination of HPV-associated head and neck cancers by birth

cohort –wise prophylactic vaccination or screening/diagnosis/treatment are presented in the following. Most notably, the diagnostics of occult oropharyngeal lesions that have a progression potential to OPC is difficult.

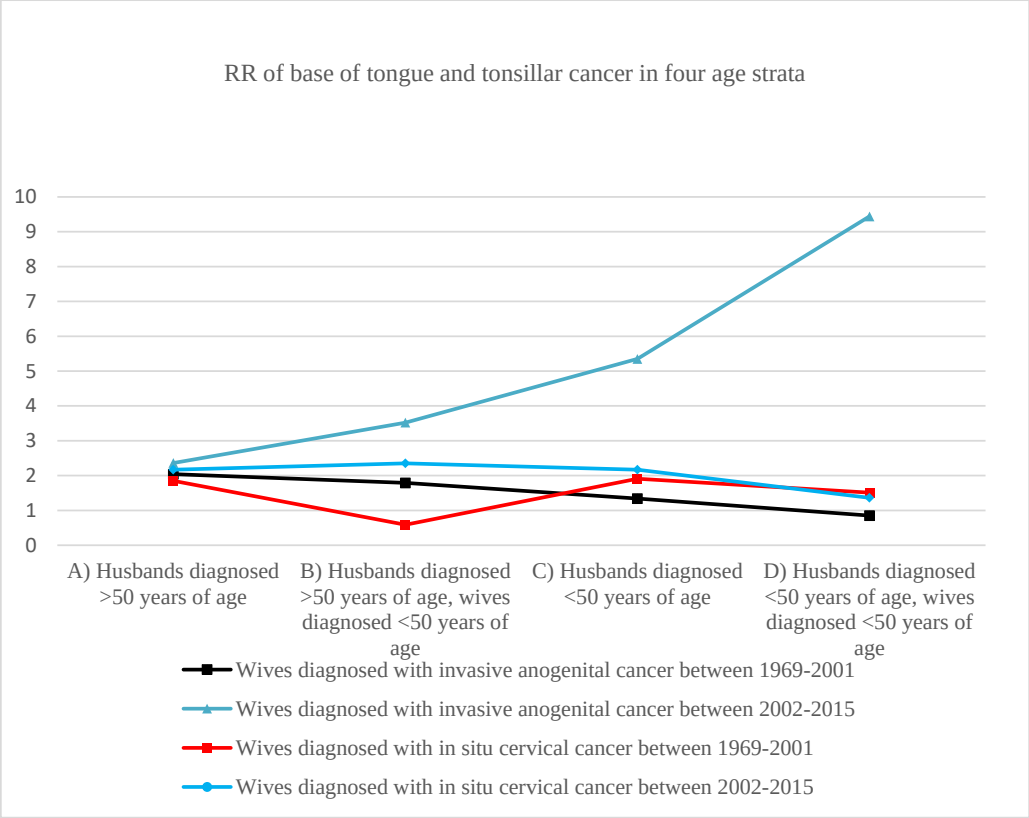

Fig. (12). Relative risk (RR) of oropharyngeal cancer in spouses of women with anogenital neoplasia (1 Invasive anogenital cancer, 2 cervical carcinoma I situ) by age and calendar time.

PREREQUISITES OF PREVENTATIVE MEASURES AGAINST HPV-ASSOCIATED OPSCC

In general, highly significantly increased relative risk (RR) estimates on the HPV16 and OPC association have been reported both in HPV serology and HPV DNA –based epidemiological studies (for reviews see [36, 169]. As for tonsillar cancer, even if it is very frequently HPV DNA positive, the serology-based RR-estimates are notably higher than the HPV DNA -based RR estimates [169]. This is in contrast to essentially comparable RR-estimates (HPV-serology or HPV DNA –based) on the association of infections with oncogenic HPV types and cervical cancer in corresponding epidemiological studies [5, 46], and deserves a comment.

ENDGAME

In the ideal world, culturally and economically feasible gender-neutral HPV vaccination of infants with a regimen comprising two vaccine shots (the latter being a mini-booster) that guarantee proper antibody response with sustainable neutralizing antibody levels will ultimately eradicate vaccine-covered oncogenic human papillomaviruses. The vacated ecological niche will be filled with other genital HPV types which, however, may lack the potential to cause lesions that would progress into cancer. For the vaccinated birth cohorts cervical screening may be restricted to once-in-a-life-time screening, and/or stopped in the foreseeable future. During the next decades this would save money and effort irrespectively of which income group countries that implement cost-effective HPV interventions belong to.

In the above-mentioned chapters, I have gone through the scientific evidence provided in a population-based fashion, most importantly from randomized controlled trials and implementation trials, in the Nordic countries on the most efficient control of HPV-associated cancers over a period of three decades. The above chapters correspond to six lectures I gave at different research institutes in two weeks last Autumn (Sep 28-Oct 12, 2023).

In Finland, the safety, immunogenicity, efficacy, effectiveness and impact (both at the individual level and population level) of the interventions were assessed in a series of randomized implementation trials mimicking alternative public health interventions. This was possible with massive help from my friends in Sweden and Germany, i.e., Joakim Dillner and Tim Waterboer. In times of trouble, high-quality analyses of tens of thousands of different DNA and serum samples stemming from the Finnish trials were analysed at the Karolinska Institute and DKFZ laboratories which maintained our independence from sponsors!

Finally, the cost-effectiveness and resilience of the interventions have been assessed with state-of-science dynamic transmission and progression models that have been fitted against the Nordic real-life data. The possibilities of predicting the forthcoming changes and rapidly correcting/fine-tuning the implemented public health interventions involving HPV infections and associated cancers are notable. In the ideal world, the Nordic countries will continue to serve as pilots for the implementation of preventative measures against HPV-associated diseases.

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Specific Webpage for the Lectures

Below are the specific web page for the lectures on which this book is based.

Chapter 1 Etiological Studies on Cervical Neoplasia

Statens Serum Institute, Copenhagen, Denmark (Nov 29, 2023)

Chapter 2 Safety, Immunogenicity and Efficacy of HPV Vaccines

Cambridge University, Cambridge, UK (Oct 4, 2023)

Chapter 3 Impact of Different HPV Vaccination Strategies

McGill University, Montreal, Canada (Oct 11, 2023)

Chapter 4 Vaccination and HPV Type-replacement

Harvard University, USA (Oct 6, 2023) and Montreal University Canada (Oct 10, 2023)

Chapter 5 Screening and Triage of Cervical Neoplasia in HPV Vaccinated Women

(Amsterdam Free University, Amsterdam, The Netherlands (Oct 2, 2023)

Chapter 6 Screening of HPV-associated Oropharyngeal Cancers

(Deutsches Krebsforschungszentrum, Heidelberg, Germany (Oct 12, 2023)

Videotaped replicas of the lectures and power point slides can be found at www.rokotiitus.net

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This book represents the culmination of a lifetime of vigorous research work led by Dr Matti Lehtinen. It is structured in six logical chapters that describe the essential discoveries by his team over the years. As a molecular epidemiologist, the author has contributed to our understanding of human papillomavirus (HPV) infection as the central causal agent in cervical cancer. Through his innovative randomized controlled trials, Dr Lehtinen also addressed key questions related to cervical cancer prevention: how to assess HPV vaccination efficacy and how best to deploy it in populations. Through a combination of empirical research and mathematical modelling, his team also examined the potential for unintended consequences from HPV vaccination. The book delves into the complex issue of type replacement post-vaccination and provides cautionary messages for policymakers everywhere. His work goes beyond primary prevention. Building on the wealth of resources from his randomized controlled trials in Finland, Dr Lehtinen also shares his lessons about how cervical cancer screening must be optimally deployed in the post-vaccination era.

Throughout the book, readers will find evidence of Dr. Lehtinen's insightful and often provocative solutions to assist the world in eliminating cervical cancer. But he goes much further; his book also paints an optimistic outlook for the prevention of oral cancers caused by HPV.

The book is accompanied by abundant ancillary documentation, providing additional insights and data on the research methods, results, and implications. Whether the reader is a technically savvy cancer prevention researcher or a scientist from a different field, this book has enough material to inspire everyone.

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