HPV Prevention and Control Board

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

30 November- 1 December 2017, Dublin, Ireland
Meeting Report

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The HPV Prevention and Control Board (https://www.uantwerpen.be/en/projects/hpv-prevention-control-board/) convened its second country meeting in Dublin, Ireland to discuss the prevention and control of human papillomavirus (HPV) and HPV-related cancers in both Ireland, a country with a recent outburst of anti-vaccine activism leading to a dramatic decrease in vaccine coverage, and the United Kingdom (UK), a country that has managed to achieve and maintain high vaccination coverage, with associated vaccine impact and effectiveness. Several topics were discussed: the current healthcare systems, HPV epidemiology (burden of disease, existing surveillance and population-based studies), as well as HPV prevention efforts, achievements and challenges in Ireland, the UK, and globally. The meeting included four roundtable sessions focusing on: what are important issues to take into account when considering gender-neutral vaccination; what should be the research topics to anticipate challenges and maintain good coverage; lessons learned from Ireland and UK to mitigate a crisis; how to articulate and convey success of the vaccine programme to support future engagement and to overcome spurious claims.

The healthcare system

Ireland

Ireland is a small country with a population of 4.8 million inhabitants and a gross domestic product of 51,000 Euro per capita (2015). The Irish healthcare system has universal coverage for hospital care. The general population pays privately for routine outpatient care and community services while a select, means tested subgroup receives free general medical services. Financial barriers for voluntary insurance and long wait times for secondary care create inequities in healthcare access. In Ireland, per capita health care spending is higher than the European Union (EU) average largely due to out-of-pocket payments and private health insurance.

United Kingdom

The UK consists of four countries: England (population: 53 million; GDP per capita: 42,700 Euro), Scotland (population: 5.3 million; GDP per capita: 31,400 Euro), Wales (population:3.1 million; GDP per capita: 21,900 Euro), and Northern Ireland (population: 1.9 million; GDP per capita: 21,800 Euro). Each country has its own system of publicly funded healthcare, but with large similarities. Public health services (including those related to school health, sexual health, drug and alcohol) are commissioned locally, but some clinical services are commissioned at the national level, including immunisation and screening programmes.

Epidemiology, burden of disease, surveillance of HPV-associated cancers

Ireland

The Irish National Cancer Registry was established in 1991, to collect and classify information on all cancer cases that occur in the Republic of Ireland. This includes monitoring cancer-related trends and outcomes and producing annual and short reports on cancer trends.

In May 2017, the HPV-associated cancer trend report for Ireland was published detailing the number of cases, incidence over time, and age-specific rates of six HPV-associated cancers (cervical, vaginal, vulvar, penile, anal/rectal and oropharyngeal cancers) diagnosed between 2010 and 2014 [1]. As cancer registries do not routinely collect information on the presence of HPV DNA in cancer tissue, the proportion of HPV-associated cancers attributable to HPV were estimated. Based on this data, each year in Ireland there are an estimated 420 HPV-associated cancer cases (265 cervical cancers, 69 oropharyngeal cancers, 32 anorectal cancers, 26 vulvar cancers, 20 penile cancers and 8 vaginal cancers) , of which 335 occur in women and 80 occur in men and result in 130 deaths per year [1].

Incidence trends over time (1994-2014) have shown that HPV-associated cancers generally increased, especially anorectal cancer (on average 3 - 4% annually). A rise in oropharyngeal cancer incidence occurred in both genders with women experiencing a yearly increase of 3.6% across the whole period, and men experiencing a 3.7% annual increase between 1999 to 2014.
In contrast, cervical cancer incidence has shown a significant decrease in the period between 2010 and 2014. The most recent, still unpublished, data confirm the ongoing downward trend in cervical cancer incidence in Ireland, suggesting the cervical cancer screening programme, initiated in 2008 is having an effect on incidence [1].

United Kingdom

To investigate the HPV type specific prevalence in cervical cancer diagnosed in England, Scotland, Wales and Northern Ireland [2], 1225 cervical cancer and 2268 cervical intraepithelial neoplasia (CIN)3 specimens were tested. Among cervical cancer cases, 95.8% were positive for at least one high-risk (HR) HPV type. The prevalence of HPV16 and/or HPV18 was 83.0%, whereas HPV types 31, 33, 45, 52 and/or 58 (i.e. the additional types in the nine-valent vaccine) were detected in 16.1% of HR HPV-positive cervical cancers. For HR HPV-positive CIN3 cases, HPV16 and/or HPV18 in 77.2% of the cases in the youngest age group, HPV31, 33, 45, 52 and/or 58 in 36.3% in those aged <30 years at diagnosis. This aligns well with global estimates, indicating that 530,000 new cases of cervical cancer occur per year, of which 96% are associated with 13 high-risk (HR)-HPV types (i.e. 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and of those 71% (or 370,000 cases) are associated with HPV types 16 and/or 18 [3].

Formalin-fixed paraffin-embedded (FFPE) tissue blocks from 2,303 women aged 16-93 years throughout Northern Ireland were collated between April 2011 and February 2013. HPV DNA was amplified by PCR and HPV genotyping undertaken using the Roche(®) linear array detection kit. HPV type-specific prevalence was 48.1%, 65.9%, 81.3%, 92.2%, and 64.3% among CIN 1, 2 and 3, squamous cell carcinomas, and adenocarcinoma cases, respectively. In 7.8% of squamous cell carcinomas, no HPV could be detected [4], likely due to the use of FFPE material [5].

In Northern Ireland, in the period 2102-2016, 9.4 cases of cervical cancer occur per 100,000 women, or approximately 88 cases per year (Northern Ireland Cancer Registry,

http://www.qub.ac.uk/research-centres/nicr/). Similarly, in this period, 117.9 cases of cervical carcinoma in situ (including CIN3) occur per 100,000 women. In the period 2000-2011, 130-215 cases of oropharyngeal cancer were diagnosed annually. Of these, 40.5% was positive by immunohistochemistry for the tumour marker P16. There is a lack of data available on the burden of vulvar, vaginal, penile, or anorectal cancer or other HPV-associated cancers in Northern Ireland.

HPV vaccination programmes

Ireland

In August 2008, it was decided to start HPV vaccination in Ireland in September 2009. However, due to poor economic conditions, the introduction of the vaccination programme was postponed leading to a lot of media coverage stating that girls were left unprotected. Partly due to this media pressure, a school-based vaccination programme began in May 2010 using the quadrivalent HPV 6/11/16/18 vaccine, aimed at 12-13-year-old girls. In the first four years, the programme easily reached its vaccination coverage goal of 80%, and 97% of girls who started vaccination, completed their course. However, in 2015, due to anti-vaccine group actions and media coverage, vaccine uptake plummeted to 50%, leaving 15,000 girls unvaccinated. The major concerns were about vaccine safety, and lack of information.
In response to the vaccine crisis, the Health Service Executive liaised with stakeholders including: the Irish Cancer Society, the National Cancer Screening Service, the Department of Education, as well as schools, national Parents Councils, and politicians. The HPV Vaccination Alliance (http://hpvalliance.ie) was established in August 2017, as an umbrella body of over 35 organisations, including the Irish Cancer Society, the National Women's Council of Ireland, the Children's Rights Alliance, the Royal College of Physicians, the Union of Students in Ireland and many others, committed to promoting HPV vaccine by providing the real facts surrounding this vaccine.
Training of health professionals was organised, and an information campaign was run, aimed at parents, all with strong support from politicians, especially the Minister of Health. This led to an increase in uptake of the first dose of HPV vaccine in the schoolyear 2017/2018.

United Kingdom

In 2008, an HPV vaccination programme for adolescent girls was introduced, targeting girls aged 12 to 13 years, largely through a school-based programme. The bivalent HPV 16/18 vaccine was used in a three-dose schedule until 2012 at which time the programme switched to use of the quadrivalent HPV 6/11/16/18 vaccine. In 2014, the programme was modified to a two-dose schedule, with the second dose provided at either 6 or 12-months after the initial dose. Since the start of the programme a coverage of around 90% has been reached, with around 85% of girls completing the course [6]. Similar coverage has been experienced in Wales (86% of girls completing the course [7]), and even slightly higher coverage in Scotland (89% of girls completing the course [8]) and Northern Ireland (91% of girls completing the course [9].

In 2016, a pilot programme for the protection of men who have sex with men (MSM) started in 42 genitourinary medicine (GUM) and human immunodeficiency virus (HIV) clinics targeting men aged ≤45 years. The pilot has been extended to 2018 but is intended to be rolled out to all GUM and HIV clinics in the UK. In Scotland, HPV vaccination of MSM in GUM settings initiated in July 2017.

Northern Ireland

Because Northern Ireland and Ireland have free movement of people, it is common to cross the border to go to school or work. Furthermore, Irish TV and newspapers are readily available in Northern Ireland, and Facebook and twitter messages are easily accessible. Hence, the Irish vaccine crisis may have led to a significant drop in vaccine coverage in Northern Ireland: from >85% in 2015 to <75% in 2017. These drops were most significant in the regions bordering Ireland, i.e. the Western and Southern Trusts. This led to an update of the programme materials, and comprehensive training for school health teams, to make them confident to promote the vaccine.

Cervical cancer screening programmes

Ireland

While the cancer registry data show an encouraging reduction in the number of new cervical cancer cases, the rate in Ireland is still high compared to other countries [10]. The national screening programme was started in 2008, and participation was boosted by the "Jane Goody effect", the death of an English television celebrity due to cervical cancer. HPV testing was added for post-treatment follow-up, and for triage of atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL). The cervical screening register benefits from integration with various other sources: colposcopy clinics, smear takers, and laboratories. HPV vaccination data are also integrated with the cervical cancer screening data. The programme reached its target coverage of 80% of the 1.2 million women aged between 25 and 60 years, although older women (50+) have been more difficult to reach. A transfer from cytology to HPV primary screening is planned to occur in the coming years, because of its higher negative predictive value, leading to fewer screens in a woman's life. As a first step a health technology assessment was performed [11], identifying the ideal strategy, age range and screening intervals. Next, the change in practices will need to be well communicated, with information, education and learning resources for all stakeholders.

England

In 2013, HPV Primary Screening Pilots sites commenced in England. In 2016, the National Screening Committee recommended that HPV Primary Screening should replace cytology as the primary screening test in cervical cancer screening programmes. The aim is for HPV primary screening to be fully implemented by end of December 2019. It is proposed to use a 5-year screening interval for women aged between 25 and 49, and a 10-year interval between ages 50 and 64. Women with an HR-HPV positive test in conjunction with normal cytology will be managed as follows: in case of persistence of HPV types 16 and/or 18 with normal cytology at 12 months, women are referred to colposcopy. In case of persistence of other

HPV types with normal cytology, women will have a repeat test in another 12 months, with referral to colposcopy if still HPV positive. The use of self-sampling for HPV to improve coverage among non-attenders will be further explored.

Wales

Wales converted fully to Liquid Based Cytology in 2005. In 2014 HPV testing was introduced for 'Test of Cure' and 'Resolution of Uncertainty.' In 2016, HPV testing was extended to include triage of low-grade abnormalities. In 2017, an HPV primary screening pilot started, comprising 20% of the screening workload, including 73 general practices and 4 laboratories, evenly distributed throughout Wales. So far, 12% of the samples have been HPV positive, and the referral rate is 4.2%, compared to 4.1% with cytology-based screening. The pilot programme is in the process of being evaluated which will be used to inform the full roll-out process.

The impact of HPV vaccination on cervical cancer screening in Scotland

HPV vaccination will have, and already has, an impact on HPV prevalence and type distribution in the population [12], as well as on the prevalence of cytological abnormalities and histologically confirmed disease of all grades. Data on this have been published for the females vaccinated as part of catch-up and will be published for those vaccinated routinely. The performance cytology screening tests may deteriorate in vaccinated women, because of the low prevalence of abnormalities in this population [13]. The increased sensitivity of primary screening via HPV testing by highly standardised and validated assay systems can mitigates, to an extent, the issue of changed cytology performance although there is initial evidence that the specificity/PPV of HPV testing will reduce given the lower attributable fraction of 16/18 infection as a proportion of remaining hr-HPV infection.
This emphasises the case for robust triage tests for HPV primary screening. Here, cytology may still play a role, because of its high specificity. Reductions in HR-HPV vaccine types in the population reduces the impact of genotyping as a triage tool. An urgent need remains, for a test that reflects the biological end-point, based on genetic changes, such as methylation.

Self-sampling in Scotland

A systematic literature review [14] showed that signal amplification tests showed lower sensitivity and specificity on self-obtained compared to clinician-obtained samples. However, validated PCR assays showed similar sensitivity and specificity on self-obtained and clinician-obtained samples. The aim of the PaVDaG (PApillomaVirus Dumfries And Galloway) Study [15] was to analytically optimise HPV detection of self-collected vagina and urine samples using the Cobas 4800 HPV test, by clinically validating HPV detection using self-collected vaginal and urine samples, according to the guidelines for sensitivity for CIN2+ not below 90%; a relative specificity for CIN2+ not below 98%.; and intra- and inter-laboratory reproducibility should be performed based on at least 500 samples, of which >30% tested HPV positive. Findings showed that among 5318 women aged between 20 and 60 years, 11% of cytologically normal individuals were positive for hr-HPV. The relative sensitivity and specificity of the vaginal sample versus the cervical sample (for CIN2+) was 0.96 (95%CI -0.94-1.00) and 0.98 (95%CI - 0.97-0.99), respectively. Very similar results

were obtained for CIN3. Finally, vaginal swabs maybe preferable over cervical smears, first because they have a lower potential for morbidity, and second, because in older (post-menopausal) women, vaginal samples (whether self- or clinician- obtained) may be more informative than cervical samples, leading to fewer unsatisfactory results.

Achievements and challenges

Communication and the HPV vaccine, what do parents and teenagers think

A survey was performed in England between July and August 2017, to explore the attitudes towards the HPV vaccine of young people aged 13 to 15 years and their parents.
Recall of immunisations was higher amongst parents and young people who had seen at least one National Health Service (NHS) leaflet (62% and 52% versus 41% and 16% who had not seen a leaflet). Concern about teenage vaccination was greater in parents and young people who used the internet to find information. The trust of social media as a source of information among both parents and young people was lower than expected. On the other hand, a total of 7% of parents and 6% of young people perceived application of at least one vaccine in the national immunisation programme to be worse than the disease the vaccine is intended to prevent. The perception of HPV vaccine safety did not differ from that of other vaccines. One-third of the parents, and one-fifth of the young people were concerned about the ingredients of the vaccine. Parents and teenagers generally agree on whether or not to be vaccinated, although more than 50% of the teenagers prefer their parents to make the decision(s) regarding vaccination.

Health Care Workers' attitude to HPV vaccination

Numerous studies highlight the importance of medical professional recommendation to maintain vaccination rates. However, in the Irish situation, anecdotal evidence suggested lack of support for vaccination among nursing and allied health care workers (HCW). To assess the HCW attitude to HPV vaccination, a short anonymous survey was circulated in 3 Dublin hospitals in 2017. Only 50% of HCW supported HPV vaccination, and among those with eligible children only 28% had consented to HPV vaccination. Even among those caring for patients with an HPV-associated cancer, only 54% supported HPV vaccination. Media coverage did not seem to have a major impact on support.

Anal cancer screening

Analogous to cervical cancer, anal cancer is preventable – a pre-malignant stage is recognisable - and progression of disease can be observed, however recent studies of anal intraepithelial neoplasia (AIN) in MSM have highlighted some key limitations in our understanding of the natural history, treatment, and screening test performance required for an optimal screening programme:

- The ANALOGY study – Manchester – feasibility and acceptability of screening. 284 MSM (203 HIV+; 81 HIV-) in a sexual health clinic in Manchester were tested by: liquid-based cytology (LBC), digital rectal examination, high resolution anoscopy (HRA) with targeted biopsy, P16 immunohistochemistry, and HPV testing. 25% had

AIN2+ and 6% had AIN3+, but sensitivity and specificity of LBC were moderate, and while sensitivity of HPV testing was high, specificity was very low [16].

- SPANC – Sydney - study of the prevention of anal cancer. A community-based natural history study of anal HPV infection and HSIL in 617 gay men (both HIV positive and HIV negative), aged 35 years and older. Men were recruited from community-based settings in Sydney, Australia, and studied using cytology, HRA, with biopsies at each of 5 visits over 3 years (baseline, 6, 12, 24, 36 months). The baseline prevalence of HSIL (cytology and/or biopsy) was 37.7%; 32.3% in HIV-negatives, and 47.3% in HIV-positives. At 6 months 70%, and at 12 months 55% of HSIL lesions persisted [17, 18].

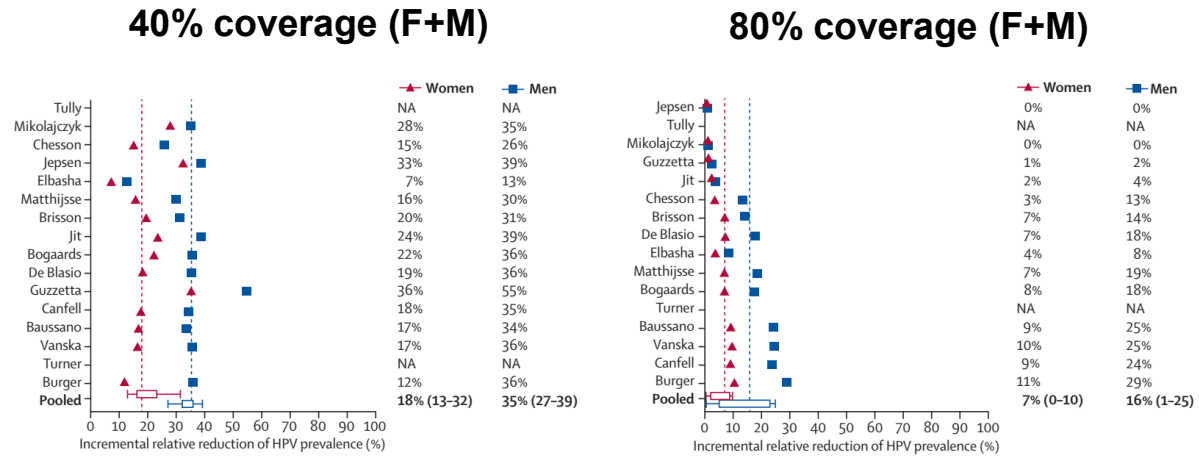
These studies showed that several requirements for screening were not met: the natural history of the condition is not adequately understood; no accepted and effective treatment for patients with recognised disease is available; facilities for diagnosis and treatment are not available; no agreed policy is available on whom to treat as patients, including the management of borderline disease [19].

However, there is still a rationale for targeted vaccination of MSM: MSM will not benefit from the herd protection effect of vaccinating 12-13-year-old girls; HPV 16-associated anal cancer is more common in MSM compared to heterosexual men; incidence of anal cancer is highest in HIV positive MSM; hence, MSM would benefit from a direct effect of vaccine – both to prevent HPV-related cancer and genital warts (depending on the vaccine used). Finally, although HPV prevalence in MSM is high, the vast majority of MSM would benefit from protection against one or more of the vaccine types [20].

Gender neutral vaccination

When vaccine coverage is low, extending vaccination to males can have a larger impact on HPV prevalence in the population. It can achieve faster and greater reduction in HPV infection in females (by indirect protection), as well as faster and greater reduction in HPV infection in males (by direct and indirect protection). However, the incremental cost-effectiveness of male vaccination increases rapidly with higher coverage in females. Figure 1 shows the incremental impact after 70 years of vaccinating males in addition to females in high-income countries, based on data obtained from a meta-analysis of 16 transmission dynamic models [21].

Figure 1. Incremental impact of vaccinating males.



Source: Brisson, Lancet Public Health 2016 [21].

Furthermore, gender-neutral vaccination maintains high protection over about 5 years of impaired coverage [22]. So, while vaccinating females with an efficacious and long-lasting HPV vaccine at high levels of coverage will protect most heterosexual males through herd immunity, gender-neutral vaccination will increase protection if coverage is low, will protect MSM, will improve resilience to temporary reductions in coverage, and will eventually be necessary for eradication of vaccine-type HPV.

The way forward

To discuss the way forward, four roundtable sessions were conducted, each focusing on one of the following four topics which are summarised below:

- What are important issues to take into account when considering gender-neutral vaccination

Gender-neutral vaccination is a matter of impact, cost and cost-effectiveness: it is necessary to look at projected disease levels, not just current disease burdens. This raises a number of questions: Are current analyses covering all the appropriate costs? What proportions of cancer are attributed to HPV, and to specific HPV types? Is vaccination of girls adequate to provide herd immunity? What is the impact of men who have sex with unvaccinated women (i.e. the fluidity of male sexuality)?

What are we trying to achieve through HPV vaccination programmes? Control, elimination, or eradication. Complete eradication would reduce costs of screening, etc., but eradication is challenging, given the large number of HPV types.

Currently, girls alone are bearing the burden of vaccination; society is relying on girls to take responsibility for sexual health (although this can also be seen as empowerment). Equality and equity, as well as ethics and law play a role in the decision to promote gender-neutral vaccination: inclusion of boys as a matter of principle, is it unlawful to exclude boys?

It was suggested that in countries that still have to start vaccination, the programme could target only boys, as long-term carriers of the virus. Data have shown that the vaccine is so effective that vaccination of one gender suffices, which makes the programme less costly. Furthermore, parents seem less worried about safety when vaccinating boys.

Finally, messaging is important, when aiming for gender-neutral vaccination, the vaccine should be seen as a general anti-cancer vaccine (rather than anti-cervical cancer vaccine, as it is currently perceived).

- What should be the research topics to anticipate challenges and maintain good coverage

Potential research topics were discussed by the panel members and divided in four sections:

– Basic science

The use of HPV vaccines as therapeutic interventions, for instance in the case of recurrent respiratory papillomatosis, should be further investigated.

– Vaccination – updating existing information

Further insight into the mechanism of effect in the immunised populations is needed, including exploration of dosage schedules (1 dose versus 2 doses, with 1 dose being especially useful in low- and middle-income countries), and a comparison of herd immunity versus gender-neutral vaccination. Furthermore, to preempt vaccine resistance, the safety of the HPV vaccines should be monitored closely and objectively, showing the public there is no reason for concern (or action is undertaken immediately if a reason for concern pops up). Finally, now that the impact in the general population becomes clear, extension of vaccination to at-risk populations, e.g. transplant recipients, should be investigated, as these will not benefit from the vaccination programme.

– Implementation of HPV testing strategies

The conclusion that the influx of vaccinated women into the screening programme necessitates a different screening algorithm leads to several topics for further research: the definition of the optimal screening strategies in immunised populations; further exploration of the role of self-testing in these strategies; and the development of the most suitable triage test.

– Understanding the dynamics of HPV infection

Natural history studies are needed to better define HPV transmission, including non-sexual transmission. Similarly, factors encouraging cervical infection, including auto-inoculation following sampling, need to be examined. This information can be used to optimise communication to promote understanding of HPV, and the need for uptake of HPV control strategies, including vaccination.

- Lessons learned from Ireland and UK to mitigate a vaccine crisis

The onset of REGRET (Reactions and Effects of Gardasil Resulting in Extreme Trauma) was the primary cause and focal point of the HPV vaccine crisis in Ireland. However, Ireland is beginning to avert the crisis, as described above. In retrospect, there is a sense that the key public health actors did not work as they should have when things were going well. The initial enthusiasm for the vaccine led to complacency, which made the crisis possible. The power of social media was not recognised, and the upcoming harm of the anti-HPV vaccination lobby was underestimated. There was a sense that as GPs were not involved in the school-based programme, they were initially unaware of the issues. This was addressed by running training programmes, e-learning courses, fact sheets and articles in journals but this should have been done earlier. The public health authority initially felt that they should hold public meetings in the areas most affected but this backfired due to disruption by REGRET supporters during town hall information meetings, resulting in heightened anti-vaccine sentiment. Furthermore, public perception, fuelled by REGRET, was that Merck was promoting the HPV vaccine for financial gain. Public health authority should have refuted this immediately. An interesting discovery from focus groups was that the Irish general population respected the official position from World Health Organization more than that from the Irish public health officials.

Suggested actions:

- Be more proactive. Early response is essential! Do not neglect signals indicating a decline in vaccination coverage
- Do not think that the problems will go away by themselves; actually, they may get worse.
- Foresee a budget for communication and education. Unlike the situation for other vaccine-preventable diseases the public has little perception of the importance of HPV infection. This calls for information campaigns.
- Importance of knowledge translation: bring science to the public.
- Resources are needed to track the sentiment of the many vaccination stakeholders.
- Track keywords indicating vaccine programme trouble being discussed in social media and adopt a proper framework for surveillance of social media. Revisit the record of social media to identify critical intervention points.
- Show empathy: public health officials must show respect and acknowledge the symptoms/syndromes of those affected by them. The plea from families of alleged victims must not be ignored. MDs and nurses who sympathise will eventually find an opportunity to communicate with victims and their families and better understand the concerns.
- GPs should be compensated for the (extra) time they need to educate girls and parents on HPV vaccination.
- Establish channels of communication, including informative websites; they can be used to guide surveillance of reactive messages in social media.
- Target individuals for debate and engagement who were affected by REGRET and not REGRET members themselves. Undecided/hesitant parents can still be convinced of the value of the vaccine, whereas REGRET members will not be convinced, regardless of the strength of the arguments.

- In the written and televised press demand airtime to dampen/ control the erroneous messages from REGRET. Prepare short videos with testimonials from people with public credibility. Try to quell concerns about conspiracy theories in the media.
- Health education is paramount. Create E-learning modules for training public health actors and teachers. Teachers are the line of first resistance against anti-vaccine activism.
- Restore confidence among public health staff. They were initially unsure about the adverse events and thought they were real and much worse. Have clear messages circulated within the first response team.
- In school-based vaccination programmes, one must prepare messages on a timely basis and establish close links with school officials.

- How to articulate and convey success of the vaccine programme to support future engagement and to overcome spurious claims

Tell emotive stories - involve cancer survivors, family members left behind, - describe the severity of the disease and the real life impact the disease can have to the individuals and their families -- be sure to hit emotions before sharing actual data. Tell success stories – numbers of cancers avoided – and how many people would get cancer if one doesn't vaccinate. Be more assertive and confident in your presentations when appropriate, even if your scientific training works against bold statements because the public reads "we are 98% sure" as "they are not sure and the opposite is possible."

Face-to-face communication is very important, therefore we need to make sure that HCW can talk about the issue appropriately: reach as many staff as possible; teach them stories to tell too, as the opposition is very good in story-telling.

Ideally, we will reach many groups—politicians, (local) journalists, clinic administrative staff. This is resource-intensive, so we must find ways to cost-effectively amplify and expand correct messaging.

Lessons learned

As safety is one of the major concerns potentially leading to vaccine hesitancy, the language of safety reporting needs to be changed. The public currently does not understand this language, so it may create confusion.
Furthermore, it is wise to acknowledge that there are girls with highly disturbing health problems, regardless of whether these problems are associated with vaccination or not. The health care system currently provides no way to support and treat these girls. This could be solved by working towards a care pathway, to provide a place to go. After all, those that feel "unheard" will oppose vaccination more vehemently.
When combating vaccine resistance, engage cancer survivors, as they are the strongest advocates of HPV vaccination. If an international network of cancer survivors is built, they can coach and inspire each other.

Perform annual attitude surveys among HCW, as a predictor of what is to come (HCW in the broadest sense, all active in vaccination field, including administrative staff who pick up the phone, as they will receive questions as well).

In countries that do not have gender-neutral vaccination, prevention of anal cancer by vaccination of high risk populations is possible. For instance, 2/3 of MSM would profit from protection against one or more vaccine types. On the other hand, more evidence is needed before implementation of anal cancer screening can occur.

The coming years will see an influx of vaccinated women into the screening system in countries that have HPV vaccination in their immunisation programme. To retain adequate sensitivity to detect premalignant lesions, a switch to HPV primary screening will become necessary, At the same time, given the relatively low specificity of HPV tests, there is a need for a triage test, however, it is as yet unclear which test is optimal.

As the general understanding of the immune system is limited, it might be good to develop a children's book on immunisation, because what is taught at the age of 7 will stick for life. Similarly, even at the professional level there is room for improvement. In general, the medical curriculum is too focused on cure, and not enough on prevention. This can partly be ameliorated by organising Europe-wide summer courses on vaccinology. Most of the medical students that attend these summer courses will not have had that information during their curriculum.

Conclusion

If prepared well in advance, a successful immunisation programme can be achieved with high vaccination coverage rates. And high coverage rates will inevitably lead to evidence of impact and effectiveness of vaccination, as shown in the UK.
On the other hand, even when experiencing anti-vaccine activism, the momentum can be regained, with support from a wide range of stakeholders, including government officials, as shown in Ireland.

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