

Population Health Improvement Directorate

Health Protection Division

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Ms Sigrid Robinson
Assistant Clerk
Public Petitions Committee
Room: T3.40
The Scottish Parliament

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Dear Ms Robinson

CONSIDERATION OF PETITION PE01574

I refer to the request of 30 October 2015 from the Public Petitions Committee for a response to written questions on a number of matters relevant to the petition. Responses to specific questions are set out below:

1. What is the Scottish Government's view on what the petition calls for?

The petition calls for “a roundtable discussion at Edinburgh between medical professionals and scientists from both sides of the debate to consider the safety of the HPV vaccines in greater detail”.

Medicine safety is a reserved matter, where the Medicines and Healthcare products Regulatory Agency (MHRA) acts on behalf of the whole of the UK to take forward issues around the licensing, safety and efficacy of medicines and functions.

The theme of the discussion for which the petitioner has asked takes place on an ongoing basis worldwide, as vaccine safety is reviewed and reconsidered by both medical professionals and scientists. It would be unlikely that new evidence would be brought to light at the roundtable requested which is not already available and which the MHRA have not factored into their decision-making.

The evidence which has been reviewed, and continues to be reviewed, by the bodies from whom the Scottish Government and the other UK administrations take their advice, shows that the HPV vaccine has a good safety profile, and is effective.

2. Is there any monitoring (formal or informal) underway in Scotland as to the safety of the HPV vaccines and the Scottish Government's HPV vaccination programme?

As with any new vaccine, Health Protection Scotland perform adverse event monitoring of a number of conditions specifically to understand the position in Scotland and have recently completed a study with the results of that monitoring. The study is being considered for publication in the peer reviewed journal, Internal Medicine, and the findings will also be considered by the WHO Global Alliance for Vaccines and Immunisation meeting in early December. However, in advance of the study's publication I have been authorised to share some of the key findings.

HPS used linked hospital admissions data from Scotland to assess the impact of the HPV vaccination programme on the incidence of 60 different conditions listed on the MHRA list of conditions that were anticipated to be possibly linked to HPV vaccination. These data was used to assess whether introduction of the bivalent and quadrivalent HPV vaccines in Scotland were associated with an increase in hospital admissions for 60 conditions.

Admission rates in boys were assessed for each diagnosis to act as a comparator as they are not currently eligible for the HPV vaccine in Scotland.

It should also be borne in mind that the rates of hospitalisation for any condition can fluctuate over time depending on referral patterns, changes in diagnostic coding, coding accuracy, natural fluctuations in disease incidence and changes in the awareness of conditions among clinicians. Consequently, any changes in incidence must be interpreted with caution.

Of the 60 different conditions assessed by HPS, 54 diagnoses **did not** increase in incidence in 12-18 year olds following the initiation of the HPV immunisation programme. This included Postural Orthostatic Tachycardia Syndrome (POTS - a condition where the heart rate increases abnormally after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain and weakness) which did not increase over expected levels in any of the years assessed and numbered 12 episodes in total (2004 - 2014).

Six diagnoses showed small increases in incidence: Bell's palsy; type 1 diabetes; coeliac disease; juvenile rheumatoid arthritis; demyelinating diseases; and ovarian dysfunction (a collection of disorders including polycystic ovary syndrome and hormonal production disorders).

- Bell's palsy: incidence increased slightly in girls, however, not over expected levels of incidence between 2004 and 2012. Additional analyses on Bell's palsy cases reported from 2012 to 2014 showed that 12 out of 28 girls (43%) were aged 12-13 when diagnosed; of whom four had received the vaccine. The remaining cases had an average time between first dose of vaccine and diagnosis of Bell's palsy of over 2.5 years.
- Type 1 diabetes, coeliac disease and juvenile rheumatoid arthritis: incidence exceeded expected levels in only 2011. Admission rates of coeliac disease

and type 1 diabetes increased in boys in the same time period. The increase in type 1 diabetes and coeliac disease in both boys and girls suggests other factors are involved in the increase of these diseases.

- Demyelinating diseases (including multiple sclerosis (MS)) increased over expected levels in 2010 and 2011 but was not associated with vaccination. Incidence of MS remained within expected levels when analysed. However, increases have also been observed worldwide, especially in countries at higher latitudes ¹.
- Ovarian dysfunction: incidence did not exceed expected levels in girls aged 15-19 between 2004 and 2014, however, there was an increase in incidence over expected levels in at least one year in women in the 20-34 age group who are currently ineligible for the vaccine, suggesting other factors were involved in the increase.

It should also be noted that Scotland is not alone in seeing increases in incidences of these conditions. The global increase in autoimmune disease, type 1 diabetes and coeliac diseases is possibly due to increased genetic susceptibility; environmental and/or lifestyle factors.

In summary, while incidence of six conditions showed an increase following the introduction of the HPV vaccine, only rarely did any increase exceed expected levels. Nor were these increases specific to girls ≤ 18 . As with all vaccines, rare adverse effect incidents can occur. However, evidence to date suggests that both the bivalent and quadrivalent HPV vaccines have a good safety profile and are effective.

The Committee will also be interested to note that the efficacy of the HPV vaccine has also been monitored and since the programme was first introduced in Scotland in 2008 it has already begun to show encouraging and positive signs of preventing the occurrence of cervical cancer, caused by the HPV virus. In August 2014 researchers at Health Protection Scotland and University of Strathclyde published their results in the British Journal of Cancer which provided further evidence to suggest that the bivalent human papillomavirus (HPV) vaccination is leading to a reduction in cervical abnormalities among the target population in Scotland.

The researchers had been monitoring the impact of the HPV vaccine since its introduction, among women attending for cervical screening at age 20. By linking the individual vaccination, screening and HPV testing records, they were able to determine the early impact of the immunisation programme on pre-cancerous cervical disease. Cervical intra-epithelial neoplasia (CIN) is when there are changes in the surface (squamous) cells of the cervix. These changes can be graded based on the likelihood of the changes leading to cervical cancer. CIN1 is least likely to develop into cancer and CIN3 is most likely to develop into cervical cancer. At the population level, researchers found that 3 doses of vaccine was associated with a 55% reduction of CIN3, a 50% reduction of CIN2 and a 29% reduction of CIN1 in those women fully vaccinated as part of the catch-up campaign. This was notable because it is likely that some of those women would

have had sexual experience prior to immunisation and it is known that the vaccine is more effective in those who have not been sexually active (hence why we offer it from age 11). This suggests that as the routine cohort of girls come through from December 2015, i.e. those immunised in 2008 who were aged 12/13, the effect of the vaccine will be even more profound and that the reductions in CIN1-3 (both low and high-grade disease) will be greater than the 29-55% reductions already seen. This is also likely to be the case because the uptake of vaccine in the routine cohort is 91% compared with 75% in the catch-up cohort.

Since the initiation of the HPV vaccination programme in Scotland in 2008, approximately 800,000 doses of the bivalent (Cervarix) and quadrivalent vaccine (Gardasil) have been administered to girls aged ≤18 years old to end 2014. Scotland's small population (~5.3 million) makes it logistically easier to implement and monitor the impact of an immunisation programme. Scotland achieved a very high uptake of three doses of the HPV vaccine and following the change in schedule to 2 doses in September 2014 maintains a high uptake in both doses. Statistics published by Information Services Division Scotland (ISD) on 17 November 2015 show that uptake across Scotland is well over 80% and is expected to increase as girls who did not start or complete their course of HPV immunisations in 2014/15 will be offered the vaccine in 2015/16. The increase in uptake can be anticipated as data shows that for pupils still in the three-dose programme, by the end of 2014/15 uptake of the second dose was 92.5%, and 88.8% for the third dose, which may infer that girls rarely experience adverse events following the first or second dose.

<https://www.isdscotland.org/Health-Topics/Child-Health/Publications/2015-11-17/2015-11-17-HPV-Immunisation-Summary.pdf?48644655943>

3. Have Scottish Government ministers received a briefing on the reviews underway in Ireland, Denmark, France and Japan into the safety of the HPV vaccinations?

Scottish Government Ministers take their advice from the relevant expert committees and regulatory bodies who monitor emerging evidence and international experience. To date those bodies have not recommended that any alteration to current policy is required.

Scottish Government Ministers have not received a specific briefing on each of the reviews underway in different parts of the world, although obviously officials from both the Scottish Government and HPS monitor latest developments around vaccine news and safety around the globe.

In respect of the Japanese position, I append at **Annex A** a link to a letter co-authored by Scottish and Japanese epidemiologists which was published in December 2014 in the Japanese Society of Internal Magazine. The letter was in response to the Japanese study which purported to show that the vaccine caused POTS in Japan. The letter points out that the Japanese study utilised poorly defined study criteria and symptoms, resulting in a misleading and false outcome.

In respect of the Danish situation, a review of HPV vaccines was initiated on 9 July 2015 by the European Commission at the request of Denmark, under Article 20 of Regulation (EC) No 726/2004. On 5th November 2015 the European Medicines Agency published its safety review of the HPV vaccine, specifically looking at two adverse drug reactions: Complex Regional Pain Syndrome (CRPS) and (POTS). These syndromes are recognised to occur in adolescence (and other age groups) regardless of vaccination status.

As with all medicinal products with a single EU-wide licence (known as 'centralised' products), the European Medicines Agency (EMA) co-ordinated this safety review. Its safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), oversaw the review. The UK (MHRA) took the overall lead in the assessment.

The review considered clinical trial data, worldwide reports of these syndromes following administration of the HPV vaccine and the available published literature. It also considered reports and testimonies submitted to EMA from a range of patient groups, including the Petitioner's organisation: the 'Association of HPV Vaccine Injured Daughters' (AHVID). The review also took account of overlap between CRPS, POTS and CFS (chronic fatigue syndrome). The review concluded that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil-9) and development of CRPS or POTS. The PRAC stated that there is no reason to change the way the vaccines are used or amend the current product information.

On 20th November 2015, the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, confirmed that it was adopting the PRAC's final opinion. The European Commission will now consider this and is expected to issue a final decision which is a legally binding decision applicable in all EU Member States. A link to the full report is appended in **Annex B**.

In addition to the European Medicine Agency review of the HPV vaccine, I also append at **Annex C** a link to a paper by the European Centre for Disease Control which reviewed the safety of the HPV vaccine and published its findings on 18 February 2015. The report concluded: "*Both HPV vaccines available are generally safe and well tolerated. Efforts should be made to increase the vaccination coverage of these vaccines as an important tool to decrease the disease burden of HPV.*"

While not specifically addressing the Irish or French positions, the Global Advisory Committee on Vaccine Safety published a statement available at: http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HP_V_12_Mar_2014.pdf on the safety of the HPV vaccine in March 2014 (which was accepted by the World Health Organisation and published on their website), which also addressed the matter of using aluminium in the vaccine as an adjuvant, which the Petitioner raised as having been an issue in France.

4. To what extent does the Scottish Government follow the MHRA's advice and guidance on HPV vaccine safety?

The Scottish Government takes its advice on vaccination issues from the Commission on Human Medicines (CHM), Medicines and Healthcare products Regulatory Agency (MHRA), Joint Committee for Vaccination and Immunisation (JCVI), Health Protection Scotland (HPS), Public Health England (PHE) and the Scottish Chief Medical Officer. No single body is relied upon for its recommendation, and the Scottish Government is careful to take a balanced view of the advice available regarding efficacy and safety before deciding on the most appropriate vaccination policy for Scotland.

5. What are the figures for reported adverse effects from an HPV vaccination in Scotland since the Scottish Government's HPV vaccination programme was introduced?

The MHRA advise that they have received a total of 552 spontaneous suspected adverse reaction reports which originated in Scotland in association with the HPV vaccine from the beginning of the vaccination programme up to and including the 13/11/15.

It is important to note that the inclusion of a particular reaction in a report submitted to the MHRA does not necessarily mean it has been caused by the vaccine, only that the reporter had a suspicion it may have. More than 8 million doses of HPV vaccine have been given in the UK, with over 90% of eligible teenagers vaccinated. With this very high level of vaccine uptake, reports of suspected adverse reactions are to be expected. But the vaccine is not necessarily the cause, and coincidental illness is a factor. Every report is taken seriously and these will remain under review. If new risks are confirmed, appropriate action will be taken to minimise such risks.

6. What advice is given to medical practitioners (such as nurses and general practitioners) in Scotland as to how to identify and report adverse effects from HPV vaccination?

As with all vaccines, GP's are directed to the Green Book *Immunisation Against Infectious Disease* for instruction on how to administer the vaccine, assess for contraindications and report any adverse effects. The chapter on the HPV vaccine provides advice on adverse effects reported by patients when the vaccine has been administered.

The Committee will also wish to be aware that in addition to the advice available to the medical profession administering the vaccine, patients are also given advice about the vaccine and the potential risks. Before obtaining consent, girls are provided with a copy of the Patient Information Leaflet for the HPV vaccine which is available on ImmunisationScotland.org, and is appended at **Annex D**.

In conclusion, all the available evidence shows that the HPV vaccine has a good safety profile and is effective. If at any time surveillance information suggests that the safety profile of the vaccine is changing then we would of course consider the implications of that immediately. However, until there is credible, objective scientific and peer-reviewed evidence that the risks of HPV vaccination outweigh the benefits,

the CMO and the Scottish Government will continue to support the HPV vaccination programme in Scotland.

I hope this information is helpful

Yours sincerely,

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Health Protection Team

[1] Alonso A, Hernán MA. Temporal trends in the incidence of multiple sclerosis: A systematic review. Neurology 2008;71:129-135.

Annex A

2015 The Japanese Society of Internal Medicine:

https://www.jstage.jst.go.jp/article/internalmedicine/54/15/54_54.4479/article

ANNEX B

European Medicines Agency Review of HPV Vaccine - November 2015:

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/11/WC500196352.pdf

ANNEX C

ECDC HPV vaccine safety submission:

<http://www.tandfonline.com/doi/full/10.1517/14740338.2015.1013532>

ANNEX D

Patient Information Leaflet:

<http://www.medicines.org.uk/emc/PIL.19033.latest.pdf>