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Influenza Vaccination

This briefing paper provides an introduction to the subject of influenza vaccination. It gives an overview of the operation of the annual vaccination programme in Northern Ireland and then looks at selected issues related to influenza vaccination. These include influenza vaccination uptake in the UK, vaccination effectiveness and cost effectiveness of vaccination. The detailed science behind measuring influenza vaccination effectiveness is complex and is touched on in the briefing. The briefing acknowledges the work that is underway in improved influenza vaccine development for the future and highlights that in the interim support will remain for current influenza vaccines as a mainstay in the reduction of influenza morbidity.

Key Points

Prevention is considered to be the most effective method of reducing the socio-economic burden of influenza and **immunisation remains the most common approach**. Influenza vaccines are usually three component vaccines (trivalent), containing two influenza A and one influenza B subtypes. The World Health Organisation monitors flu viruses throughout the world and each year makes recommendations about the strains to be included in the vaccine for the forthcoming winter.

In terms of the **operation of the annual influenza vaccination programme** each year in Northern Ireland (NI), the DHSSPS sets out the process and it is co-ordinated via GP practices to those over 65 and for those under 65 in identified clinical risk groups.

For 2011/12, the target uptake of the vaccine for the over 65s remains at 75%, while for the under 65 at risk group it has been raised from 60% in 2010/11 to 70% for 2011/12. Figures compiled by the Health Protection Agency (HPA) indicate that the programme would appear to be operating well in NI (see Table 1), with NI performing at least as well, and mostly better, than other jurisdictions of the UK in vaccinating both the over 65s and under 65s in clinical risk categories.

Based on a **cost-effectiveness** study (unpublished at time of writing) conducted by the HPA, the UK Joint Committee for Vaccination and Immunisation (JCVI) recently concluded that the current seasonal influenza vaccination programme is "*highly likely to be cost-effective compared with no vaccination, particularly when considered over a number of years, but for some individual years there may be little benefit to vaccination when the influenza season is mild, or the vaccine is not well-matched to the prevalent strains*".

The JCVI also concluded that, on the basis of the current HPA study, extending vaccination to children aged five to under 17 years or to children aged six months to under 17 years, is likely to be cost-effective. However, additional analyses are still required and the economic benefits come from "*mostly reducing influenza transmission from children to adults rather than from protecting children themselves*".

In terms of **best practice**, the UK, like many developed countries, organises a large-scale annual influenza vaccination campaign to vaccinate all people aged 65 years or older, and those under 65 in clinical 'at risk' groups. Internationally, the United States goes the furthest with its vaccination campaign. From 2010 it established the first recommendation of national universal seasonal flu vaccination with trivalent inactivated vaccine recommended for all individuals aged 6 months and older and live attenuated influenza vaccine for healthy (non-pregnant) people aged 2-49 years.

In terms of **vaccine effectiveness**, recently published reviews and a meta-analysis of many influenza vaccine studies indicate moderate estimates of clinical effectiveness of current influenza vaccinations. The need for vaccines with improved immunogenicity

compared with those currently available is well recognised. New vaccines based on novel antigens that differ from the presently licensed vaccines are in development.

Researchers have highlighted that, **based on a track record of substantial safety and moderate efficacy in many influenza seasons, current influenza vaccines must continue to have a role in the reduction of influenza morbidity until more effective interventions are available.**

1. Introduction

Influenza, more commonly referred to as 'Flu', is a very contagious, airborne respiratory tract infection. Although generally considered to be a self-limiting disease[1], influenza is associated with considerable morbidity and mortality worldwide. Influenza affects all age groups and infection is associated with increased use of healthcare resources, absenteeism from work and loss of productivity, even among otherwise healthy adults.

With seasonal influenza, elderly individuals and those with underlying medical conditions, such as cardiovascular or respiratory disease, appear at greatest risk of developing life-threatening complications of influenza, such as pneumonia.[2] However, during an influenza pandemic (the emergence of a new influenza virus to which many people have no pre-existing immunity), such as that caused by influenza H1N1 (2009), the virus caused most of its severe or fatal disease in younger people, both those with chronic conditions as well as healthy persons.[3]

Prevention is considered to be the most effective method of reducing the socio-economic burden of influenza and immunisation with inactivated virus remains the most common approach. In addition, public health campaigns advise individuals to take appropriate hygiene measures, for example the UK *Catch it, Bin it, Kill it – Respiratory and Hand Hygiene Campaign (2011)*.[4]

Every year, large-scale campaigns in many developed countries are undertaken to vaccinate at least all people aged 65 years or older to prevent serious illness and mortality, as an estimated 90% of all seasonal influenza-related mortality occurs in this group.

The United States goes the furthest with its vaccination campaign and in 2010 the Advisory Committee on Immunization Practices (ACIP) established the first recommendation of national universal seasonal flu vaccination with trivalent (three component) inactivated vaccine[5] recommended for all individuals aged 6 months and older and live attenuated influenza vaccine[6] for healthy (non-pregnant) people aged 2-49 years. This universal vaccination recommendation came after a decade of

[1]Self-limiting disease – one which usually stops or ends without therapy or assistance, however medical treatment will assist in relieving pain or discomfort and hospital treatment may be necessary, http://www.ehow.com/facts_6863624_self_limiting-mean_.html

[2]Hannoun, C, Megas, F and Piercy, J (2004), Immunogenicity and protective efficacy of influenza vaccination, Virus Research, 103, 133-138

[3] Pandemic H1N1 (2009), WHO, FAQ http://www.who.int/csr/disease/swineflu/frequently_asked_questions/post_pandemic/en/index.html

[4]Catch it, Bin it, Kill it - Respiratory and hand hygiene campaign (2011), Department of Health, http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123234

[5] Inactivated vaccine - An inactivated vaccine is one that uses a dead or killed virus, http://asthma.about.com/od/preventioncontrol/f/faq_inactivated.htm

[6] Live attenuated vaccine - **Live vaccines** contain weakened forms of the organism that causes the disease. Such organisms are also called **attenuated,** www.who.int/vaccine.../tb/vaccine.../live_attenuated/en/index.html

incremental changes during which the ACIP expanded recommendations to include an ever increasing proportion of the US population.[7]

Influenza vaccines are usually trivalent, containing two influenza A and one influenza B subtypes.[8] The World Health Organisation (WHO) monitors the epidemiology of flu viruses throughout the world and each year makes recommendations about the strains to be included in the influenza vaccine for the forthcoming winter. For the 2011/12 vaccine the composition is[9]:

- An A/California/7/2009 (H1Ni) – like virus;
- An A/Perth/16/2009 (H3N2) – like virus; and
- A B/Brisbane/60/2008 – like virus.

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI)[10] is responsible for recommending which groups should receive influenza vaccination. The JCVI annually updates 'The Green Book' in preparation for the next influenza vaccination programme[11],[12]. In February 2011, the JCVI agreed the following additions to the programme for 2011/12[13]:

- All pregnant women should be offered seasonal influenza vaccine irrespective of trimester of pregnancy, as they are at risk from influenza during all stages of pregnancy and are to be considered to be in a clinical risk group for seasonal influenza vaccination;
- Severe neurological disability should be added to the examples listed under 'chronic neurological disease' in the table of clinical risk categories, as this was risk factor for influenza; and
- Since the summary of product characteristics for seasonal influenza vaccines are currently unclear about the dose of vaccine for young children, the Green Book should indicate that a full dose of vaccine should be administered to children from six months of age as there is evidence from a recent study that this dose is effective in young children.

The DHSSPS confirmed in a published letter HSS(MD) 14/2011 the list of eligible patients who should be offered the seasonal flu vaccine in Northern Ireland (see Appendix 1, as extracted from the letter HSS(MD) 14/2011) and highlighted that, as advised by the JCVI, all pregnant women should be offered vaccination by their GP,

[7] Osterholm, M. T., Kelley, N. S., Sommer, A. and Belongia, E. A. (2011), Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

[8] Hannoun, C, Megas, F and Piercy, J (2004), Immunogenicity and protective efficacy of influenza vaccination, Virus Research, 103, 133-138

[9] The Seasonal Influenza Vaccination Programme 2011/12, Chief Medical Officer, DHSSPS, 25 July, 2011, HSS(MD) 14/2011

[10] JCVI - an independent expert advisory committee that advises Ministers on matters relating to the provision of vaccination and immunisation services, http://www.dh.gov.uk/ab/JCVI/index.htm

[11] The Green Book is the popular name for *Immunisation against infectious disease* which is a publicly available document on the principles, practices and procedures of immunisation in the UK.

[12] The Green Book, http://www.dh.gov.uk/en/Publichealth/Immunisation/Greenbook/index.htm

[13] JCVI, Minute of the Meeting held on Wednesday 2 February 2011, page 11 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_127779.pdf

and GPs should ensure that those with chronic neurological disease are (especially children and young people) are prioritised.[14] The DHSSPS advise that the list is not exhaustive and that medical practitioners should apply clinical judgment.

In addition, front line Health and Social Care workers are "*strongly recommended to take up the offer of vaccination to protect themselves, their families and vulnerable patients in their care*". Vaccination is carried out by the Occupational Health Service in each Trust.[15]

2. How the Influenza Vaccination Programme Operates in Northern Ireland (2011/12)

The DHSSPS letter HSS(MD) 14/2011, issued in July 2011, as mentioned above, set out the process of the vaccination programme. The process is as follows, (summarised from HSS(MD) 14/2011):

The process begins with the central procurement by the Public Health Agency of the seasonal influenza vaccine and these were available for GP practices to order by mid-August 2011.

The vaccination programme officially began on 3 October 2011 and will run until the 31 March 2012; however GPs were at liberty to commence vaccinations as soon as they had received their first delivery of vaccine.

Under the arrangement associated with the 'GMS contract financial envelope', the Health and Social Care Board (HSCB) has already been allocated funding for the vaccination of over 65s and for those under 65 in clinical risk groups. Additional money will be allocated in 2011/12 to the HSCB from the Public Health Agency (PHA) to cover payments to GPs for the vaccination of carers and pregnant women.

For other patients requesting or requiring a vaccination, if the GP agrees to the vaccination, then a health service prescription should be written and dispensed from the community pharmacy from the commercial pharmaceutical supply chain.[16]

Publicity and information materials were launched in September/ early October 2011 to encourage those in the clinical risk groups as well as health and social care workers and unpaid carers to take up the offer of a vaccine. Funding is provided to allow GPs to decide how best to contact their patients.

For 2011/12, the target uptake for the over 65's remains at 75%, while the uptake rate target for the under 65 at risk group has been raised from 60% in 2010/11 to 70% for

[14] The Seasonal Influenza Vaccination Programme 2011/12, Chief Medical Officer, DHSSPS, 25 July, 2011, HSS(MD) 14/2011

[15] The Seasonal Influenza Vaccination Programme 2011/12, Chief Medical Officer, DHSSPS, 25 July, 2011, HSS(MD) 14/2011, paragraph 5

[16] Contractually it is not possible for GPs to charge for such a prescription or for the administration of the vaccine to a patient registered with the practice.

2011/12 (the 60% target last year was to allow the 'Apollo System', now used to identify these patients, time to 'bed in').

The responsibility for achieving high uptake in frontline health and social care workers lies with the HSC Trusts. Community Pharmacists, staff involved in supplying medicines, frontline private nursing and residential home staff will also be able to receive the vaccine from the Occupational Health Service in their local Trust. The PHA will collect data on vaccine uptake in health and social care workers on a weekly basis.

At the end of this season's influenza programme, the PHA will audit the number of vaccines delivered to practices and the number recorded as used. A similar analysis last year showed that in a number of instances vaccine was lost due to cold chain[17] failures. The DHSSPS expect all practices to have in place arrangements to ensure wastage is low.

3. Issues for Consideration

3.1 Influenza Vaccination Uptake in the UK

Table 1 below shows the seasonal influenza vaccine uptake in the UK in 2009/10 and 2010/11 seasons and illustrates that the uptake in Northern Ireland is good when compared to the rest of the UK.The data is extracted from the Health Protection Agency Publication *Surveillance of influenza and other respiratory viruses in the UK, 2010/11* (May 2011).[18]

[17]The "cold chain" refers to the continuum of safe handling practices, including materials, equipment and procedures, that maintain vaccines within the required temperature range from the time they are manufactured to the time they are administered to patients, http://www.cmaj.ca/content/171/9/1050.full

[18]http://www.hpa.org.uk/Publications/InfectiousDiseases/Influenza/1105influenzareport/

Table 1 Seasonal Influenza Vaccine Uptake in the UK in 2009/10 and 2010/11 Seasons.

	Proportion of Group Vaccinated (%)			
Vaccination Group	**Northern Ireland**	**England**	**Scotland#**	**Wales**
Over 65 years 2010/11	74.9	72.8	75.4	65.8
Over 65 years 2009/10	77.0	72.4	75.0	63.5
Under 65 years at risk 2010/11	78.7	50.4	56.1	48.6
Under 65 years at risk 2009/10	80	51.6	53.3	49.1
Healthy pregnant women 2010/11	59.9*	36.6	64.9	39.7
Pregnant women at risk 2010/11	Data not collected	56.6	74.8	55.3

*Calculation based on May 2010 to March 2011 figures

Subject to validation by National Services Scotland

Table 2 below (directly extracted from *Surveillance of influenza in Northern Ireland 2010/11*, Public Health Agency, 12th September 2011[19]) gives more detailed figures for Northern Ireland for the last three influenza seasons.

[19] http://www.publichealth.hscni.net/publications/surveillance-influenza-northern-ireland-2010-11, page 16

Table 2: Seasonal flu vaccine uptake 2008–09 – 2010–11

Northern Ireland GP flu vaccine coverage data			
	To 31 March 2009	To 31 March 2010	To 31 March 2011
	2008/09	2009/10	2010/11
Number of practices	358	357	355
Number of practices submitting return by 31 March	314	357	355
Number of 65+ receiving flu vaccine between 1 October and 31 March	170,818	201,052	198,505
Registered 65+ population of practices submitting a return	222,484	261,628	265,123
Uptake rate for 65+ population at 31 March	**76.8%**	**76.9%**	**74.9%**
Number of under 65 at risk population receiving flu vaccine between 1 October and 31 March	104,607*	147,903	152,712
At risk population under 65 years from practices submitting a return	141,301	184,986	193,939
Uptake rate for under 65 at risk population at 31 March	**74.0%**	**80.0%**	**78.7%**

Note: slight differences in figures due to rounding of numbers.

****Population in 2009 was taken to be 10% of the under 65 year old population.***

At the end of March 2011, the total number of vaccines given in Northern Ireland was greater than in the previous year. The reason the numbers have risen while the percentages have fallen slightly is that more people are being identified as eligible for the vaccine as there are both more elderly people and more people being identified in the other risk groups.[20]

[20] *Surveillance of influenza in Northern Ireland 2010/11*, Public Health Agency, 12th September 2011 http://www.publichealth.hscni.net/publications/surveillance-influenza-northern-ireland-2010-11

3.2 Influenza Vaccination Effectiveness

3.2.1 What is Vaccine Effectiveness?

It is thought that currently available inactivated influenza vaccines offer substantial protection against influenza, particularly in terms of limiting disease severity and reducing the potential for serious complications.[21]

There appear to be two main aspects to the effectiveness of the influenza vaccine.

Firstly, there is the overall effectiveness of the vaccine depending on how well matched the trivalent vaccine and the circulating viruses are in any given influenza season. According to the US Centers for Disease Control and Prevention in years when the vaccine and circulating viruses are well matched, "*influenza vaccines can be expected to reduce laboratory-confirmed influenza by approximately 70% to 90% in healthy adults under 65 years of age*". In years when they are not well matched vaccine effectiveness can be lower;

> *"For example in a study among persons 50-64 years during the 2003-04 season, when the vaccine strains were not optimally matched, inactivated influenza vaccine effectiveness against laboratory-confirmed influenza was 60% among persons without high-risk conditions, and 48% among those with high risk conditions, but it was 90% against laboratory confirmed influenza hospitalisation".*[22]

Secondly, in an individual, the effectiveness depends primarily on their age and immune competence. The effectiveness may be lower among persons with chronic medical conditions and among the elderly as compared with healthy young adults and children.[23] Other influences include use of medications and prior exposure to influenza antigens[24] whether as a result of naturally acquired infection or by previous vaccination.[25]

An additional complication is that the estimates of effectiveness vary based on the outcome that is measured. For example, two possible measurements are the prevention of laboratory confirmed influenza or prevention of influenza-associated hospitalisations.[26]

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[21] Hannoun, C; Megas, F. and Piercy, J. (2004), Immunogenicity and protective efficacy of influenza vaccination, *Virus Research*, **103**, 133-138

[22] Flu Vaccine Effectiveness: Questions and Answers for Health Professionals, Centers for Disease Control and Prevention, www.cdc.gov/flu/professionals/vaccination/effectivnenessqa.htm

[23] Flu Vaccine Effectiveness: Questions and Answers for Health Professionals, Centers for Disease Control and Prevention, www.cdc.gov/flu/professionals/vaccination/effectivnenessqa.htm

[24] Antigen - An **antigen** is any substance that causes your immune system to produce antibodies against it, www.nlm.nih.gov/medlineplus/ency/article/002224.htm

[25] Hannoun, C; Megas, F. and Piercy, J. (2004), Immunogenicity and protective efficacy of influenza vaccination, *Virus Research*, **103**, 133-138

[26] Flu Vaccine Effectiveness: Questions and Answers for Health Professionals, Centers for Disease Control and Prevention, www.cdc.gov/flu/professionals/vaccination/effectivnenessqa.htm

In order to ensure as effective a vaccine as possible, as part of the marketing approval process, influenza vaccines in Europe are tested annually for 'immunogenicity' (the ability of the vaccine to provoke an immune response in or the degree to which it provokes a response).[27] Vaccines must achieve certain increases in a specific measured antibody in vaccinated patients aged 18-60 years and in patients over 60.

The link between immunogenicity and vaccine effectiveness is clear but it is thought that it may not be straightforward due to other factors such as herd immunity (the resistance of a group to attack by a disease to which a large proportion of the members are immune) and the possibility of resistance to reoccurring influenza strains after considerable periods of time.[28]

3.2.2 Recent Published Evidence for the Efficacy and Effectiveness of Influenza Vaccination

Over the last few years the Cochrane Collaboration and the Lancet have published reviews covering the effectiveness of influenza vaccines in published studies. The Cochrane database published systematic reviews in three areas:

- Vaccines for preventing influenza in the elderly (included 75 studies)[29];
- Vaccines for preventing influenza in healthy adults (included 50 studies)[30]; and
- Vaccines for preventing influenza in healthy children (included 51 studies).[31]

The Lancet published a meta-analysis on the efficacy and effectiveness of influenza vaccines licensed in the USA (included 31 studies from a screening of 5707 articles).[32]

The studies by Cochrane and Osterholm and colleagues (The Lancet) differed in several ways. Osterholm and colleagues' meta-analysis uses the

> *"classic epidemiological definitions of efficacy and effectiveness, in which efficacy refers to the relative risk reduction attributed to vaccination as estimated from a randomised controlled trial, and effectiveness refers to the same measure of effect from an observational study"*[33]

The Cochrane reviews use efficacy to refer to the

[27] Definition of immunogenicity, http://medical-dictionary.thefreedictionary.com/immunogenicity

[28] Hannoun, C; Megas, F. and Piercy, J. (2004), Immunogenicity and protective efficacy of influenza vaccination, *Virus Research*, **103**, 133-138

[29] Jefferson, T. et. al. (2010), Vaccines for preventing influenza in the elderly, *Cochrane Database Systematic Reviews*, 2010, **2**: CD004876

[30] Jefferson, T. et. al. (2010), Vaccines for preventing influenza in healthy adults, *Cochrane Database Systematic Reviews*, 2010, 7: CD001269

[31] Jefferson, T. et. al. (2008), Vaccines for preventing influenza in healthy children, *Cochrane Database Systematic Reviews*, 2008, 2:CD004879 ,

[32] Osterholm, M. T., Kelley, N. S., Sommer, A. and Belongia, E. A. (2011), Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

[33] Kelly, H and Valenciano, M (2010), Comment, Estimating the effect of influenza vaccines, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

> *"relative-risk reduction in which symptomatic laboratory confirmed influenza is the outcome, whereas effectiveness is used for influenza-like illness. Such illness is a non-specific clinical outcome associated with a wide range of respiratory viruses"*[34]

It is thought that evaluation of influenza vaccines against non-specific outcomes, such as influenza-like illness or hospital admission due to pneumonia may confuse the understanding of the true impact of influenza and the effect of influenza vaccines.[35]

The more restrictive selection criteria for study inclusion used by Osterholm and colleagues led to differences in results from the Cochrane review. The Osterholm and colleagues' meta-analysis estimated a pooled inactivated vaccine efficacy against influenza infection in adults of 59% (95% CI 51-67)[36] compared with an estimated efficacy in healthy adults of 73% (95%CI 54-84) in the Cochrane review for years when the circulating influenza strains and vaccine strains were well matched and 44% (95% CI 23-59) in years when they were not well matched.[37]

Overall Osterholm and colleagues concluded that,

> "*evidence for consistent high level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those aged 65 years or older*".

However, in spite of that - based on a

> "*track record of substantial safety and moderate efficacy in many seasons, we believe the current influenza vaccines will continue to have a role in reduction of influenza morbidity until more effective interventions are available*".[38]

Future interventions are discussed in more detail in Section 4 below.

3.2.3 The Estimated Effectiveness of the Seasonal 2010/11 Influenza Vaccine and the Pandemic Influenza A(H1N1)2009 in the UK in 2010/11

In February 2011, the Health Protection Agency (HPA) published the results of a mid-season analysis study[39] into the effectiveness of seasonal 2010/11influenza vaccine in preventing influenza. The study covered 4,554 individuals (from whom samples were collected during the study period 1st September 2010 to 11 January 2011) who

[34] Kelly, H and Valenciano, M (2010), Comment, Estimating the effect of influenza vaccines, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

[35] Kelly, H and Valenciano, M (2010), Comment, Estimating the effect of influenza vaccines, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

[36] CI is the Confidence Interval -A confidence interval is a range around a measurement that conveys how precise the measurement is. This means that for the estimated vaccine efficacy quoted there is a 95 percent chance that the vaccine efficacy falls within the range 51%-67%. The narrower a confidence interval is the more accurate the estimate.

[37] Kelly, H and Valenciano, M (2010), Comment, Estimating the effect of influenza vaccines, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

[38] Osterholm, M. T., Kelley, N. S., Sommer, A. and Belongia, E. A. (2011), Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

[39] The study uses data from sentinel surveillance schemes in England, Scotland and Wales.

presented with an acute influenza-like illness in a participating GP practice and who were swabbed and tested positive for influenza. The control samples were similar individuals who tested negative for influenza.[40]

After adjustments for age group, month of sample collection and surveillance scheme, influenza vaccine effectiveness against confirmed influenza A(H1N1)2009 was

- 34% (95% CI: -10-60**%**)if vaccinated only with the pandemic vaccine in 2009/10;
- 46% (95% CI: 7-69%) if vaccinated only with the seasonal trivalent vaccine in 2010/11; and
- 63% (95%CI: 37-78%) if vaccinated in both seasons.

When other types of influenza (influenza A H3 or influenza B) were also considered, the seasonal trivalent vaccine, after adjustments as described above, resulted in a vaccine effectiveness of 50% (95%CI: 17-70%).[41]

Therefore vaccination with only the pandemic vaccine in 2009/10 seemed to provide the least level of protection in the 2010/11 season. This indicates that pandemic vaccination may not last across seasons and reinforces the recommendation that annual re-immunisation of target groups is required.[42]

The Health Protection Agency confirmed that the effectiveness figures found through the study were consistent with *moderately good matching* between the seasonal vaccine and circulating influenza strain and that in a poorly matching season they could be much lower. The HPA stated that 60-70% effectiveness was what was hoped for.[43]

3.3 JCVI Investigation into the Impact and Cost Effectiveness of Influenza Vaccination

At its meeting on 5th October 2011, the JCVI heard an overview from the HPA on the study it had been requested to undertake by the JCVI on the impact and cost effectiveness of the current influenza vaccination programme in the UK and the consideration of possible extensions to the programme.

In considering the unpublished HPA study, the JCVI noted some main findings in its draft minutes of the meeting[44]:

[40] Peabody, R. et. al. (2011), Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: Mid-Season Analysis 2010/11, *Eurosurveillance*, **16**(6) Article 3, www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19791

[41] Surveillance of influenza and other respiratory viruses in the UK, 2010-2011 report, Health Protection Agency, May 2011, page 55

[42] Peabody, R. et. al. (2011), Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: Mid-Season Analysis 2010/11, *Eurosurveillance*, **16**(6) Article 3, www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19791

[43] Personal telephone communication with Richard Peabody, Health Protection Agency, November 2011

[44] Joint Committee on Vaccination and Immunisation (JCVI), Draft Minute of the meeting held on Wednesday 5 October 2011, paragraph s13,14 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_131103.pdf

- The prevalence of risk factors for influenza increased markedly with age;
- Hospitalisation attributable to influenza is highest in children under six months, high in children aged six months to under five years and in adults aged 65 and over. However for those in the influenza clinical risk groups, the relative risk of hospitalisation was higher in adults than in children and highest for those aged 45-65 years;
- Mortality estimates in the HPA study were likely to be underestimated as they are based on influenza-related deaths in hospital only;
- The burden of influenza falls mostly on those who have clinical risk factors for influenza and on older people (the groups currently targeted for influenza vaccination in the UK);
- The current seasonal influenza vaccination programme is "*highly likely to be cost-effective compared with no vaccination, particularly when considered over a number of years, but for some individual years there may be little benefit to vaccination when the influenza season is mild, or the vaccine is not well-matched to the prevalent strains*" It accepted the caveats that cost-effectiveness is sensitive to estimates of influenza-related deaths and to the number of deaths prevented by vaccination; and
- The JCVI considered data from some additional analyses which suggested that increasing vaccination uptake to 75% in clinical risk groups would be beneficial (note – in Northern Ireland this is already achieved for most groups, see Table 2 above).

The JCVI concluded that, on the basis of the current HPA study, extending vaccination, to children aged five to under 17 years or to children aged six months to under 17 years, is likely to be cost-effective. However additional analyses were still required and the economic benefits come from "*mostly reducing influenza transmission from children to adults rather than from protecting children themselves*".[45]

The JCVI agreed in principle to support extension of the vaccination programme to children on the basis of the findings of the current HPA study. However this was dependent, in part, on additional analyses supporting the conclusions drawn including[46]:

- A review of data on the safety of the vaccines and on the US experience of using live attenuated intranasal vaccine for children (as there is good evidence that the live attenuated intranasal vaccine and the adjuvanated inactivated intramuscular vaccine are more effective in children that the currently available unadjuvanated inactivated vaccines);

[45] Joint Committee on Vaccination and Immunisation (JCVI), Draft Minute (until ratified at next JCVI meeting) of the meeting held on Wednesday 5 October 2011, paragraph 16 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_131103.pdf

[46] Joint Committee on Vaccination and Immunisation (JCVI), Draft Minute (until ratified at next JCVI meeting) of the meeting held on Wednesday 5 October 2011, paragraph 26 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_131103.pdf

- Further data on the contribution of children to influenza transmission to others as this is key to the impact and cost-effectiveness of their vaccination;
- Attitudinal research studies on the acceptability and hence uptake of the vaccines by pre-school children in GP practices and uptake by primary- and secondary school-age children in schools; and
- Potential costs of implementing GP and schools-based programmes.

4. Discussion and Future Directions

It is thought that currently available inactivated influenza vaccines offer substantial protection against influenza, particularly in terms of limiting disease severity and reducing the potential for serious complications.[47]However, the efficacy of these vaccines in an individual may be influenced by a range of factors, including age, health status, use of concurrent medications and prior exposure to influenza antigens (whether as a result of naturally acquired infection or by previous vaccination).[48]

Recent published reviews and a meta-analysis of many influenza vaccine studies show that the evidence for consistent high level protection is elusive for the present generation of vaccines, particularly in individuals at risk of medical complications or those aged 65 years or older. However, that being said, the researchers coming to those conclusions also highlight that based on a track record of substantial safety and moderate efficacy in many influenza seasons, current influenza vaccines must continue to have a role in the reduction of influenza morbidity until more effective interventions are available.[49]

Due to moderate estimates of clinical effectiveness of current influenza vaccinations, the need for vaccines with improved immunogenicity compared with those currently available is well recognised. New vaccines based on novel antigens that differ from the presently licensed vaccines are in development. However, it is thought that what is needed are active partnerships between industry and government to "*accelerate research, reduce regulatory barriers to licensure, and support financial models that favour the purchase of vaccines with improved protection*".[50]

[47]Hannoun, C, Megas, F and Piercy, J (2004), Immunogenicity and protective efficacy of influenza vaccination, Virus Research, 103, 133-138

[48]Hannoun, C; Megas, F. and Piercy, J. (2004), Immunogenicity and protective efficacy of influenza vaccination, *Virus Research*, **103**, 133-138

[49]Osterholm, M. T., Kelley, N. S., Sommer, A. and Belongia, E. A. (2011), Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

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In order to pursue improved vaccines the JCVI have welcomed submissions for its consideration containing additional information on the safety, immunogenicity, clinical effectiveness and duration of protection of novel influenza vaccines.[51]

A new universal influenza vaccine, called Flu-v, is in development by drug development company SEEK (London). After successful Phase 2 trials, scientists are planning large scale clinical trials. The vaccine is based on recognising a part deep inside the influenza virus that does not change and is found in all flu virus strains. Current vaccines are based on recognising the outer 'coat' of the virus and this constantly changes hence the need for new vaccines each season.[52]

Until improved vaccines are fully developed, researchers have advocated that in the interim there is a need for routine effectiveness studies of the presently licensed influenza vaccines using virus-confirmed endpoints. For inactivated vaccines, it is proposed that these endpoints should be influenza infection diagnosed by a specific technique called-PCR[53], as culture tests miss cases and serology tests alone over-estimate vaccine efficacy and effectiveness.[54]

Active pursuit of new vaccines and interim measures of improved routine effectiveness studies are recommended but in the meantime, it is generally agreed that support should remain for the present influenza vaccines and vaccination programmes that are the best intervention currently available for seasonal influenza.[55]

[51] JCVI, Call for evidence on seasonal influenza vaccines, 28 February 2011, www.dh.gov.uk/ab/JCVI/DH_124686

[52] Universal flu vaccine to end annual jabs, The Telegraph, 6November 2011

[53] RT-PCR – Reverse transcriptase – Polymerase Chain Reaction

[54] Kelly, H and Valenciano, M (2010), Comment, Estimating the effect of influenza vaccines, The Lancet, Published online at www.thelancet.com/infection on 26th October 2011

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Appendix 1 – Clinical risk groups 2011/12 (as extracted from HSS(MD) 14/2011)

Eligible groups	Further detail
All patients aged 65 years and over	
Chronic respiratory disease aged six months or older	Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission. Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children who have previously been admitted to hospital for lower respiratory tract disease.
Chronic heart disease aged six months or older	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease.
Chronic kidney disease aged six months or older	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease aged six months or older	Cirrhosis, biliary artesia, chronic hepatitis
Chronic neurological disease aged six months or older	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised (e.g. polio syndrome sufferers). Clinicians should consider on an individual basis the clinical needs of patients including individuals with cerebral palsy, multiple sclerosis and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.
Diabetes aged six months or older	Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.
Immunosuppression aged six months or older	Immunosuppression due to disease or treatment. Patients undergoing chemotherapy leading to immunosuppression. Asplenia or splenic dysfunction, HIV infection at all stages. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age) or for children under 20kg a dose of 1mg or more per kg per day. It is difficult to define at what level of immunosuppression a patient could be considered to be at a greater risk of the serious consequences of flu and should be offered flu vaccination. This decision is best made on an individual basis and left to the patient's clinician. Some immunocompromised patients may have a suboptimal immunological response to the vaccine. Consideration should also be given to the vaccination of household contacts of immunocompromised individuals, i.e. individuals who expect to share living accommodation on most days over the winter and therefore for whom continuing close contact is unavoidable. This may include carers (see below).
Pregnant women	Pregnant women at any stage of pregnancy (first, second or third trimesters).
People living in long-stay residential care homes or other long-stay care facilities where rapid spread is likely to follow introduction of infection and cause high morbidity and mortality. This does not include, for instance, prisons, young offender institutions, or university halls of residence.	Vaccination is recommended.
Carers	Those who are in receipt of a carer's allowance, or those who are the main carer, or the carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill. (Please note – this category refers to individual carers entitled to a free flu vaccine on the NHS, not professional health and social care workers who should be vaccinated by their employer as part of an occupational health programme.)