National Surveillance System for Human Papillomavirus Infection and Related Disease in Scotland

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1.0: Background

From September 2008, the Human Papillomavirus (HPV) vaccine will be included in the national immunisation schedule in Scotland with the aim of preventing cervical cancer. Immunisation will be targeted at females aged 12 to 13 years with a catch-up campaign targeted at females up to but not including 18 years. A bivalent vaccine Cervarix, manufactured by GSK will be used, that protects against HPV types 16 and 18. HPV-16 and 18 are recognised as the causative agents of over 70% of cervical cancer.

The introduction of a vaccine against HPV may over time necessitate the reorganisation of the cervical screening programme to reflect changes in the prevalence of HPV related disease (cervical abnormalities and pre-cancerous lesions) in this population. A system for monitoring HPV and HPV related disease in the Scottish population will provide data to inform what will be the optimum combination of vaccination, screening and HPV testing required to reduce the incidence of cervical cancer.

As with all national immunisation programmes there is a need to assess the impact of the HPV immunisation programme. Currently surveillance of HPV related disease is undertaken by Information Services Division (ISD) and HPS through the cervical screening programme, the cancer registry and through surveillance of genital warts. Aggregated data on cervical abnormalities for all age-groups is reported and age-specific data on cervical cancer, by 5 year age-band is reported. There is currently no surveillance of HPV infection in Scotland. The development of a national HPV surveillance system will require the instigation of pro-active specimen collection and testing for HPV and pro-active data collection on HPV related disease in those aged less than 25 years. As the vaccine chosen for the national programme targets solely the HPV types associated with cervical cancer, the surveillance of genital warts will not be included in this system.

In accordance with ECDC recommendations for the monitoring and evaluation of HPV vaccination [1], HPV prevalence in vaccinated cohorts, particularly the prevalence of persistent infections, as well as cytological and histological abnormalities will be monitored. Furthermore, at its meeting in October 2007, the Joint Committee on Vaccination and Immunisation (JCVI) endorsed an HPA paper outlining a proposal for the evaluation of the HPV Immunisation programme which had the following objectives:

1. To evaluate the effect of the HPV immunisation programme on HPV-related cervical disease and on the frequency of vaccine-type and non-vaccine-type HPV infections in women in the birth-cohorts targeted for vaccination, either as part of the routine immunisation programme or as part of the catch-up campaign, and in males and females not eligible for HPV vaccination

2. To measure vaccine effectiveness against vaccine-type HPV infections and HPV-related disease

and

3. To be prepared to investigate risk factors for, and mechanisms of, vaccine failure

HPS and its Scottish partners have agreed to dovetail Scotland's efforts with the HPA approach. In addition, the HPV Project Epidemiology and Surveillance Group have identified the need to:

4. Monitor the uptake of the routine and catch-up immunisation programmes and determine the characteristics of those who do not avail of the vaccine

5. Relate the uptake of the vaccine to any changes in the uptake of cervical screening amongst those targeted for vaccination and monitor those who default on screening and immunisation and who may therefore be at increased risk of developing cervical cancer (hard-to-reach population)

6. Monitor the rate of adverse events and other untoward consequences associated with the programme

7. Conduct qualitative work to assess changes in knowledge, attitudes and awareness to HPV and the immunisation programme after the programme is implemented nationally.

With regard to the first objective, there is a need to determine if type replacement or cross-protection against non-vaccine types is occurring and to assess whether herd immunity can be observed in males and in unvaccinated females.

The levels of ongoing protection provided by the vaccine will need to be monitored in order to inform the organisation of the HPV immunisation schedule and to identify the need for booster doses.

The surveillance activities described in this protocol will focus on meeting the first two objectives, namely the monitoring of HPV infection and HPV related disease, and to determine vaccine effectiveness in birth-cohorts offered the vaccine. As the vaccine aims to prevent cervical cancer, the surveillance activities described in this protocol will focus solely on the surveillance of females. Surveillance activities to determine herd-immunity in males will be developed at a future data and will be the subject of a separate protocol.

1.1: The HPV Immunisation Programme in Scotland

The national HPV immunisation programme commenced on 01 September 2008. All girls in secondary school year S2 (age-range 11 – 13 years) will be offered immunisation as part of the routine programme. The catch-up programme will run from 2008 for 3 years (Table 1).

The schedule requires the administration of three doses at 0, 2 and 6 months, therefore the vaccine is scheduled to be administered between September and March of each year in schools, with mop-up arrangements in place for eligible girls who do not begin or complete the course, to be conducted primarily through primary care.

Table 1: National HPV Immunisation Programme, phasing and scheduling of catch-up campaign. Table courtesy of Scottish Government Health Department.

Phasing of HPV Immunisation Catch-up Campaign in Scotland: (beginning September 2008, completing August 2011)				
Year	**School year at start of catch-up campaign: September 2008**	**Age at start of catch-up campaign: September 2008**	**School year when vaccination first offered**	**Age when vaccination first offered**
Year 1: (September 2008 to August 2009)	S5/S6/left school	16 - under 18 years	S5/S6/ left school	16 – under 18 years
Year 2: (September 2009 to August 2010)	S3/S4	13 -15 years	S4/S5 Left school	14 -16 years
Year 3 (September 2010 to August 2011)	"Mop up" of those with incomplete or no vaccination.			

1.2: Cervical Screening in Scotland

Currently the primary intervention against cervical cancer in Scotland is the population based cervical screening programme.

All women aged between 20 and 60 years who are registered with a general practitioner and therefore who have a Community Health Index (CHI) number are currently invited for cervical screening every 3 years. Invitation is by automatic call recall and is operated by the Scottish Cervical Call Recall System (SCCRS) at National Services Division. Women are called for their first screen 3 months after their 20th birthday and those who do not respond to the first initiation are sent repeat invitation for screening 3 times in that year, after which time they are considered to have defaulted on screening. Women who are not registered with a GP and who therefore do not have a CHI number may be recruited into screening from a number of opportunistic sources such as GUM clinics and family planning clinics.

During screening a liquid based cytology (LBC) specimen is taken and is sent to the designated pathology laboratory for that health board for testing. There are 11 such laboratories in Scotland covering 14 health boards. Results are reported back to the primary care practice or other health clinic via SCCRS. Previously the laboratories reported results directly back to ISD; however since May 2007 results for all smears are recorded on SCCRS.

The results from the initial screening fall into ten diagnostic categories: normal, borderline abnormality, mild, moderate and severe dyskaryosis, severe dyskaryosis with features suggestive of invasive carcinoma and glandular neoplasia / suspected glandular neoplasia, adenocarcinoma and other. The number of unsatisfactory smears is also recorded.

In the event of a borderline smear or mild dyskaryosis, the woman may be asked to attend for repeat smears or be referred to colposcopy after a single mild smear. Following 3 borderline or 2 mildly abnormal smears the woman must be referred to colposcopy for further investigation. Those diagnosed with moderate and severe dyskaryosis will be referred directly to colposcopy. Those diagnosed with severe dyskaryosis suggestive of invasive carcinoma or glandular neoplasia / suggestive glandular neoplasia are referred directly to colposcopy.

Further examination at colposcopy will indicate that either no further action need be taken, that the woman should continue to be monitored via cervical screening or that a biopsy should be taken. The results from histopathology fall into six main diagnostic categories, currently reported by ISD: cervical intraepithelial neoplasia (CIN) 1, CIN2, CIN3, Cervical Glandular Intraepithelial Neoplasia (CGIN), adenocarcinoma and cancer of the cervix uteri. CIN 2 and 3 and CGIN are always recorded on SCCRS.

Increasing degree of cytological severity corresponds to increasing likelihood of an underlying CIN and the proportions of these that are HPV positive also increases with severity. Approximately 30% of women with a mild dyskaryosis will have CIN3 as will 60% of women with moderate and 90% of women with severe dyskaryosis. Of those with mild dyskaryosis, approximately 87% are HPV positive, of those with moderate dyskaryosis approximately 92% are HPV positive and of those with severe dyskaryosis, approximately 99% are HPV positive.

There is considerable heterogeneity in the pathway of an individual through screening and an individual woman may have multiple diagnoses of cervical abnormalities from smear results and biopsies in a single year. This data is captured from a variety of sources: the primary care practice, the cytology laboratory, the colposcopy clinic and the histopathology laboratory will all report to SCCRS. SCCRS will provide a single point of streamlined data for each individual attending cervical screening and SCCRS will be the main source of data on HPV related disease for the purposes of surveillance.

Currently the numbers of abnormal smears are recorded on SCCRS. Aggregate results for all age-groups in the 10 diagnostic categories detailed

above are reported by ISD as part of their cervical screening statistics. ISD also reports cervical cancer statistics, namely carcinoma in situ of the cervix uteri – ICD-10 D06 (CIN3) and cancer of the cervix uteri – ICD-10 C53. Data on the numbers and percentages of new diagnoses of CIN1 and 2 and CGIN are not currently reported by ISD; however this data will be captured on SCCRS. This data is currently held by individual laboratories and on the National Colposcopy Clinical Information and Audit System (NCCIAS).

NCCIAS is a national information system, rolled out in 2006 with the aim of monitoring colposcopy services in Scotland against NHS Quality Improvement Scotland (QIS) standards. It collects data on patients attending colposcopy services including their demographic data, and their diagnostic and treatment history (appointments, referrals, colposcopy assessment and findings, biopsies, smear results, treatments and planned follow up care and management). It does not interface to SCCRS although it may do so in the future.

As only aggregate data for abnormal smears for all age-groups are currently reported, for the purposes of HPV surveillance, it is desirable to separately monitor the incidence and prevalence of these end-points in vaccinated birth-cohorts.

All grades of cervical abnormality of grade CIN2 and above and CGINs are categorised as high grade and are suitable surrogate end-points for cervical cancer for the purposes of HPV surveillance [1].

1.3: Monitoring the hard-to-reach population

As attendance at cervical screening is an effective intervention against the development of cervical cancer, those at greater risk of developing cancer are those who default on screening, particularly if they have also declined immunisation. We define those who default on screening as our hard-to-reach population. There is a strong socio-economic gradient in the incidence of cervical cancer influenced by multiple factors which include lower uptake of immunisation and attendance at screening with increasing deprivation.

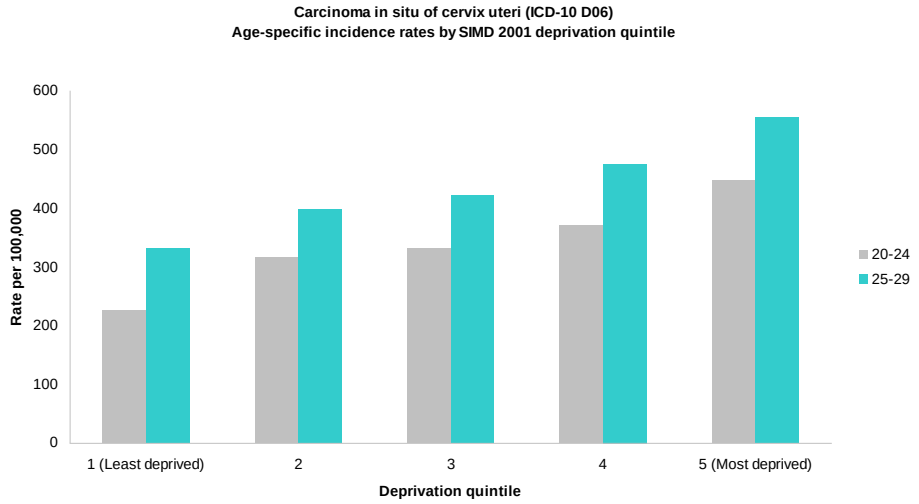
National data [3] and data from Greater Glasgow and Clyde NHS Board [4] indicates that uptake of cervical screening is lower among younger age-groups and is inversely related to social deprivation. The uptake in those aged 20 to 24 years of age is particularly low at less than 60%. Attendance may be further diminished by the introduction of HPV immunisation, particularly in older women immunised through the catch-up campaign, if they no longer perceive themselves to be at risk of cervical cancer, due to the proximity of their first invitation to screening to when they were immunised.

In Greater Glasgow and Clyde NHS Board the 5.5 year screening uptake in 2005/2006 varied from 86% in areas of lowest deprivation to 74% in the areas of highest deprivation [3]. The incidence of carcinoma in situ of the cervix uteri is strongly correlated with social deprivation in 20 to 24 year olds (Figure 1). The age-specific incidence rate for this age-group was 226.4 cases per

100,000 person years at risk in those from areas of least deprivation compared to 447.5 cases per 100,000 person years at risk in those from areas of the highest social deprivation.

Anecdotal evidence indicates that there is a degree of heterogeneity in the characteristics of those who default on cervical screening. This population is likely to include a variety of groups such as those who are at high risk of cervical cancer, who are not in contact with the health service and whose sexual health is poor; as well as those who have never been sexually active and who are at low risk of cancer.

Figure 1: Age-specific incidence rates of carcinoma in situ of the cervix uteri by deprivation category, Scotland, 2000 – 2004. Data courtesy of Donna Nicholson at ISD.



Monitoring of the cervical screening population will need to be supplemented by additional methods of monitoring the hard-to-reach population, in order to inform the development of targeted public health interventions to prevent cervical cancer in those most at risk in the era of vaccination, in particular those who decline vaccination and cervical screening.

2.0: The Public Health Goal / Service Objectives

The Goals of the system are:

- To evaluate the impact of the routine and catch-up HPV immunisation programme on the incidence and prevalence of HPV infection, HPV related disease and ultimately on cervical cancer in the Scottish population.

- To help inform decision making on the future organisation of the HPV immunisation programme and on the optimum mix of immunisation, screening and testing required to reduce the incidence of cervical cancer in Scotland.

It will do this by:

- Evaluating the effect of the HPV immunisation programme on outcomes such as:

  - The incidence and prevalence of abnormal cervical smears (borderline smears, mild, moderate and severe dyskaryosis), glandular abnormalities, pre-cancerous cervical lesions (CIN1, 2 and 3, CGIN) and invasive cervical cancer (cancer of the cervix uteri, invasive squamous cell carcinoma and adenocarcinoma) in birth cohorts offered the vaccine and the HPV types associated with these

  - The prevalence of vaccine-type and non-vaccine-type HPV infections in women of vaccinated age

- Assessing the correlation between HPV infection with vaccine and non-vaccine types with age, with social deprivation and with vaccination history

- Determining the effectiveness of the vaccination programme in reducing overall HPV infection, infection with vaccine types, pre-cancerous lesions and cervical cancer in both routine and catch-up cohorts.

3.0: Baseline Surveys to Inform Surveillance

A national prevalence survey of HPV in 11 to 18 year olds (the age-group targeted for vaccination) in Scotland has been undertaken. This survey, conducted in schools and colleges of further education will provide data on the prevalence of infection with vaccine related and non-vaccine related HPV types in the general population before the immunisation programme in this age-group begins. This data will be used as a baseline against which data from future surveillance and investigation can be compared.

Further baseline surveys will need to be conducted for each arm of the surveillance system. A phase IV study for HPV immunisation is planned for Scotland. Any baseline prevalence studies will be conducted before women vaccinated under the phase IV study enter the cervical screening programme.

4.0: Population under surveillance

The population under surveillance will include females aged from 12 years up to and including 24 years of age who are resident in Scotland. In the first instance the population under surveillance will include all females aged between 12 and up to 18 years in September 2008. Thereafter surveillance will continue to include those from vaccinated cohorts presenting for their first and second cervical smear.

We are initially defining our surveillance population as up to 24 years for a number of reasons. HPV prevalence normally declines after age 24 due to changes in sexual behaviour. Surveillance until 24 years will allow us to

monitor females through two rounds of cervical screening. Furthermore, currently screening statistics are reported in aggregated five year age-groups (20 to 24 years and 25 to 29 years). In order to enable direct comparison to our baseline population we will define our surveillance population in the same way.

The cervical screening programme provides the framework for longitudinal monitoring of birth-cohorts of women. Vaccinated women should be monitored throughout the course of their cervical screening career so that the ultimate long-term impact of HPV immunisation on the incidence of cervical cancer can be determined and so that risk factors for the development of cervical cancer in the era of mass immunisation can be identified. With this in mind we recognise that we may need to extend the period of surveillance. We will also work with our partners in ISD and the cervical screening programme to co-ordinate our surveillance activities with existing surveillance of women attending cervical screening.

Although the purpose of the system is to determine the effectiveness of the Scottish HPV immunisation programme, our study population is likely to include a proportion of females who were immunised in other parts of the UK or overseas. As these females fall under the care of the Scottish health service for the diagnosis and treatment of cervical abnormalities and cancer, they will be included in our study population, regardless of where or if they were offered vaccination, even though they will not be recorded on our national immunisation databases and therefore we will not be able to ascertain their immunisation status.

This population can be categorised as follows:

- Females who are vaccinated and who present for cervical screening,
- Females who are vaccinated and who do not present for cervical screening,
- Females who decline vaccination but do present for cervical screening,
- Females who decline vaccination and who do not present for cervical screening,
- Females whose vaccination status is unknown but who do present for cervical screening,
- Females whose vaccination status is unknown and who do not present for cervical screening,

5.0: Timeline for surveillance

It will be an average of 8 years before the first routinely vaccinated cohort of S2 females will be invited for their first cervical smear. In order to allow this first cohort to be monitored through two screening cycles, the surveillance system will need to be operational for a minimum of 12 years if baseline surveillance starts in 2008 and for 10 years if surveillance commences when the first birth cohort included in the catch-up vaccination programme (those aged 17 years and 364 days in September 2008) enters the cervical screening service (Figure 2). A full timetable for the development of the surveillance system can be found in Appendix 1.

In the first instance, the surveillance year will run from 01 January to 31 December each year. This may be changed in future or we may choose to report our results in different ways, such as by financial year or by quarter.

6.0: Data Requirements

This document will focus on the surveillance of all grades of cervical abnormalities as measured by cytology, colposcopy and histology and the HPV types associated with these as well as on the overall and type-specific HPV prevalence in females in the birth-cohorts invited for routine and catch-up HPV immunisation.

7.0: Events under Surveillance

An overview of the surveillance system is presented (Figure 3). Sample size calculations for the surveillance system were provided by Prof. Chris Robertson and are detailed in full in **Appendix 2**. The aim of the surveillance system is to determine the effectiveness of the HPV immunisation programme in the general Scottish population. This population can be divided into those who attend and those who default on cervical screening, approximately 60% and 40% of the general population of women respectively [3]. We propose strategies to obtain a representative sample of each group, which together will provide a representative sample of the whole. We will monitor these endpoints by age, gender, immunisation status and social deprivation.

Figure 2: Initial timescales for the operation of the HPV surveillance system

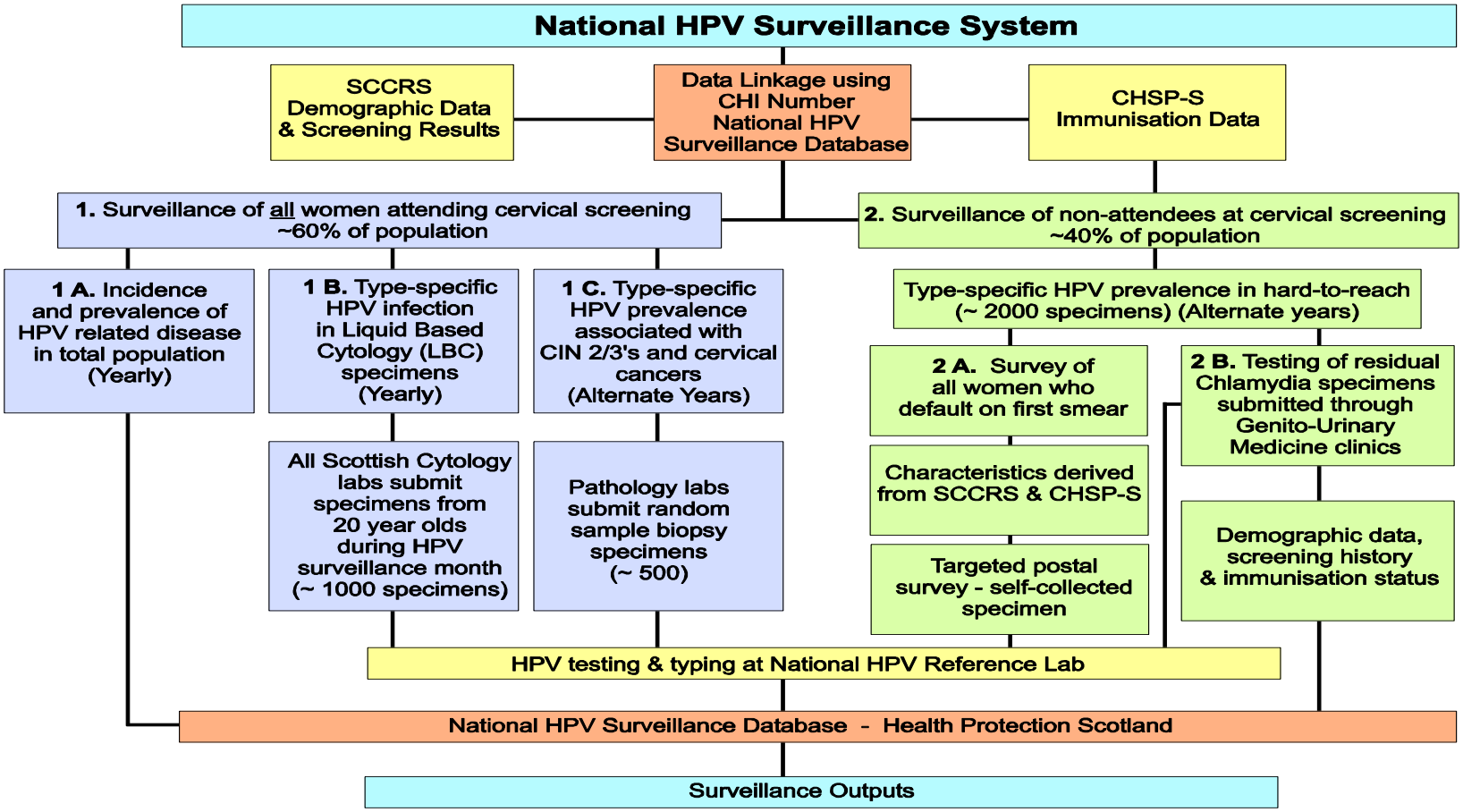
	Immunisation Group	Age at immunisation	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Catch -up	S5/S6/left school	16 - 17years & 364 days												
	S3/S4 (14/15 in 2008)	16 - 17years & 364 days												
	S2 2008	12 - 13 years												
Core Immunisation Programme	S2 2009	12 - 13 years												
	S2 2010	12 - 13 years												
	S2 2011	12 - 13 years												
	S2 2012	12 - 13 years												
	S2 2013	12 - 13 years												
	S2 2014	12 - 13 years												
	S2 2015	12 - 13 years												
	S2 2016	12 - 13 years												
	S2 2017	12 - 13 years												
	S2 2018	12 - 13 years												
	S2 2019	12 - 13 years												
	S2 2020	12 - 13 years												
	S2 2021	12 - 13 years												
	S2 2022	12 - 13 years												
	S2 2023	12 - 13 years												
	S2 2024	12 - 13 years												
	S2 2025	12 - 13 years												
	S2 2026	12 - 13 years												

Immunised

First smear

Second smear

Figure 3: Overview of Proposed National HPV Surveillance System



8.0: Surveillance of the Cervical Screening Population

8.1: Population under surveillance

Females aged up to and including 24 years, from vaccinated birth cohorts, who attend for cervical screening in Scotland.

8.2.0: Surveillance of the incidence and prevalence of abnormal smears and cervical abnormalities in all women attending for screening.

HPS will collaborate with ISD in monitoring the number and percentages of new diagnoses and the incidence of abnormal smears, of CIN 1, 2 and 3, of CGIN and of cervical cancer among cohorts invited for immunisation on an annual basis.

8.2.1: Objectives:

- To determine the effectiveness of the vaccination programme in reducing the incidence and prevalence of abnormal cervical smears, pre-cancerous lesions and cervical cancer in birth-cohorts targeted for vaccination

- To assess the correlation of HPV related disease with age, with social deprivation and with vaccination history

8.2.2: Methods:

For those diagnosed with a cervical abnormality, data on their demographic characteristics (age, post-code, health board of residence, health board of screening), as well as their cytology, colposcopy and histology results will be extracted from SCCRS and will be linked to their vaccination history as recorded on the Child Health Surveillance Programme - Schools database (CHSP-S). This process of data linkage will be undertaken by ISD. A look-up will be applied to post-code data to assign each individual with a category under the Scottish Index of Multiple Deprivation (SIMD). Post-code data and other patient identifiers will be stripped and each individual will be assigned an anonymous identification number. A complete linked database of all individuals registered on SCCRS and CHSP-S will be sent to HPS for analysis. This database will include individuals registered on SCCRS who are not recorded on CHSP-S as they were never vaccinated in Scotland and people who were vaccinated in Scotland and are recorded on CHSP-S but who have now left Scotland and who are therefore not recorded on SCCRS.

8.2.3: Baseline Data Collection / Pilot:

Baseline data on cervical abnormalities, glandular abnormalities and pre-cancerous lesions will be collected for at least 5 years prior to the first immunised birth-cohort entering the programme, thus allowing us to monitor trends in HPV related disease. Existing and new data from 2007 onwards can be collected directly from SCCRS as a pilot for the surveillance system and data prior to 2007 will need to be collected retrospectively from the laboratories. Baseline data for CIN3 and cancer of the cervix uteri is readily available from ISD for our target age-group and dates from 1980. Baseline data for CIN1 and 2 and CGIN will be collected directly from the laboratories.

8.2.4: Case Definition:
Clinically diagnosed (in accordance with Scottish Cervical Screening Programme and ICD-10 definitions) HPV-related disease: mild, moderate and severe dyskaryosis, glandular abnormality, CIN1, 2 and 3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma.

8.2.5: Proposed Dataset
Table 2: Minimum dataset for surveillance of women attending for routine cervical screening

Label	Format	Preferred Input	Description	Source of Data
Date of Specimen	Date	MM/YYYY	Patient Specimen / Screening Date	SCCRS
Age	Age	YY	Age at Screening	SCCRS / CHSP-S
Deprivation Category	Numeric	NN	Scottish Index of Multiple Deprivation Category, derived from postcode data	SCCRS / CHSP-S
Age at vaccination	Age	YY	Age at last dose of vaccine	CHSP-S
Date at last vaccination	Date	MM/YYYY	Patient vaccination date for last administered course	CHSP-S
Vaccination Status	Numeric	N	0 = unvaccinated 1 = incomplete course – 1 dose 2 = incomplete course – 2 doses 3 = fully vaccinated, completed course 4 = Status unknown	CHSP-S
Cytology Results (most severe result per individual per year only)	Numeric	N	*Cytology results* 0 = Normal smear 1 = unsatisfactory smear 2 = borderline smear 3 = mild dyskaryosis 4 = moderate dyskaryosis 5 = severe dyskaryosis 6 = severe dyskaryosis / invasive 7 = glandular abnormality 8 = Adenocarcinoma 9 = Other	SCCRS
Pathology / Biopsy Results	Numeric	N	*Pathology / Biopsy Results*: 0 = none 1= CIN 1 2 = CIN 2	SCCRS

			3 = CIN 3 4 = CGIN 5 = invasive squamous carcinoma 5 = adenocarcinoma 6 = cancer of the cervix uteri 7 = other	

8.2.6: Data Analysis & Outputs

A time-series analysis will be conducted to illustrate trends in the prevalence of cervical abnormalities and pre-cancerous lesions from baseline to post-vaccination and to demonstrate the impact of vaccination over time in the catch-up cohorts and in those immunised as part of the core programme. Changes in prevalence will be assessed using tests on proportions and logistic regression. Logistic regression will allow us to calculate odds ratios for our proposed analytical outcomes, however we can also easily calculate relative risks.

Table 3: Data analysis outputs for surveillance of women attending routine cervical screening

	Borderline/Mild / Severe Dyskaryosis / Severe Dyskaryosis-Invasive / Glandular Abnormality / Adenocarcinoma / Other Positive	**Total**	**Prevalence Rate (%)**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	CIN1/2/3, CGIN Positive	**Total**	**Prevalence Rate (%)**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						

	Pathology diagnosed Cancer of the cervix / Squamous Cell Carcinoma / Adenocarcinoma Positive	**Total**	**Prevalence Rate (%)**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						

Note: A separate output will be produced for each grade of abnormality, lesion and cancer and for each explanatory variable; these are aggregated here for the purposes of brevity.

8.3: Surveillance of HPV Infection in a Sample of Women Attending for their First Cervical Smear

The first birth cohort invited for HPV immunisation will be called for screening in 2011/2012. It is proposed that LBC specimens from a representative sample of this and subsequent cohorts should be screened and typed for HPV.

8.3.1: Objectives

- To determine and quantify the effectiveness of the vaccination programme in reducing overall HPV infection and infection with vaccine types in birth-cohorts targeted for vaccination

- To assess the correlation of HPV infection with vaccine and non-vaccine types with age, with social deprivation and with vaccination history.

8.3.2: Methods

There are 11 cytology laboratories in Scotland with responsibility for cervical screening. All cytology laboratories will be asked to submit residual specimens to the Scottish National HPV Reference Laboratory (SNHPVRL) for secondary testing for HPV. Laboratories will be recruited though the Scottish Pathology Network. We will work with the laboratories to develop a suitable strategy for specimen collection. Proposed strategies include:

1. Systematic collection of all residual LBC specimens from a specific birth cohort from a single lab from a different health board each month, to rotate through the different health boards in Scotland;

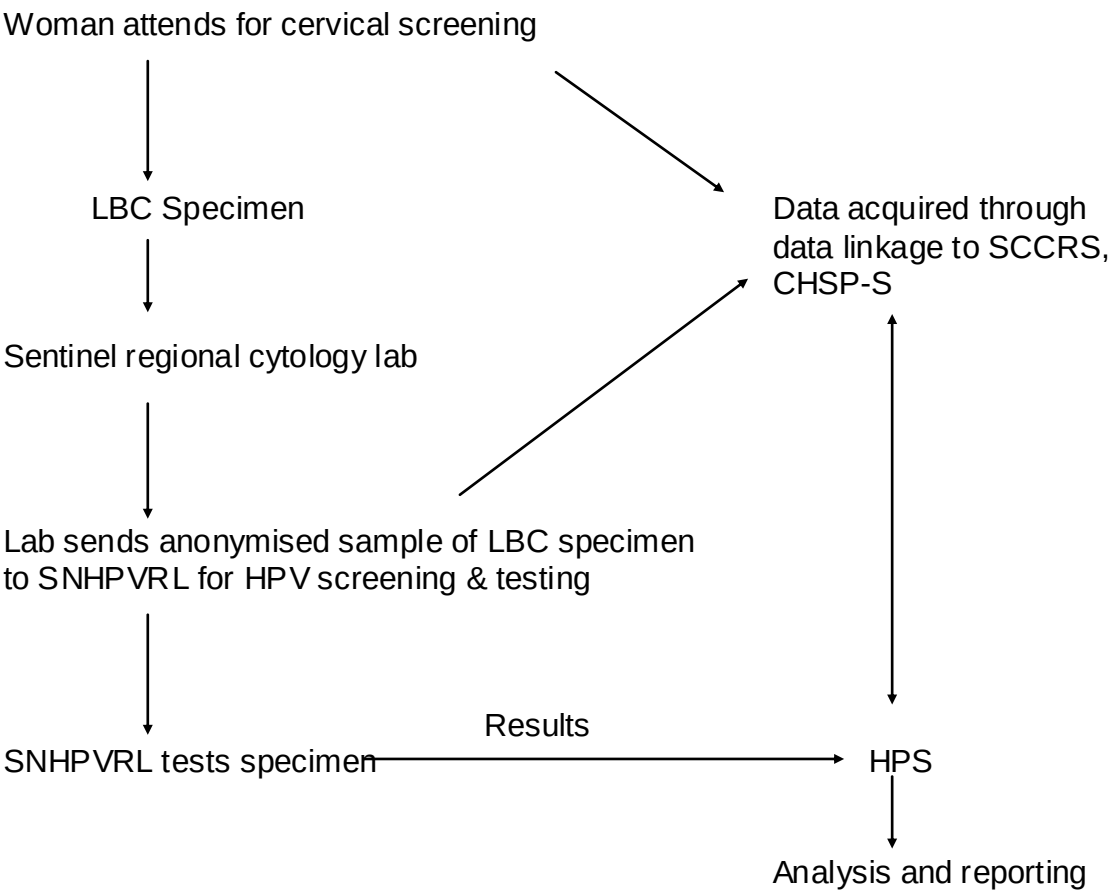
2. Collection of specimens from all labs on a specific day each month;

3. Collection of specimens from all labs over a single month of the year, with care taken to select a time-period that does not correspond to any transition weeks; for instance week 53 (end of December, start of January) or the last week of August / first week of September (incorporating two different birth-cohorts for vaccination).

The first sampling strategy is the preferred option. We will collect an additional 10% of specimens over and above the statistical sample size needed for our calculations to compensate for samples from which HPV cannot be extracted.

Data on each subject will be collected through data linkage of the subject's cytology specimen with their demographic data as collected on SCCRS and with their vaccination history as recorded on CHSP-S. Data linkage will be conducted at ISD. SNHPVRL will forward results to HPS. We will also be able to capture histology results for each individual from SCCRS.

Figure 4: Outline of surveillance of LBC specimens collected from sentinel laboratories.



8.3.2: Baseline Survey / Pilot

A representative sample of those entering the screening programme prior to the instigation of the immunisation programme will be tested using the same methodology as for the routine surveillance system to provide baseline data for this system and to pilot the methodology.

8.2.3: Case Definitions

HPV-16 genital infection: Isolation of HPV-16 DNA from a genital specimen using a validated / QC testing system

HPV-18 genital infection: Isolation of HPV-18 DNA from a genital specimen using a validated / QC testing system

High-risk (HR) HPV genital infection: Isolation of HR-HPV DNA from a genital specimen using a validated / QC testing system

Low-risk (LR) HPV genital infection: Isolation of LR-HPV DNA from a genital specimen using a validated / QC testing system

Vaccine type HPV genital infection: Isolation of vaccine-type HPV DNA from a genital specimen using a validated / QC testing system

Non-vaccine type HPV genital infection: Isolation of non-vaccine type HPV DNA (including types 31, 33, 40, 45, 51, 53, 54, 58, 59, 66, 68, 70, additional high-risk types and other unrecognised / undefined type) from a genital specimen using a validated / QC testing system

Multiple high-risk (HR) HPV genital infection: Isolation of multiple types of HR-HPV DNA from a genital specimen using a validated / QC testing system

Multiple low-risk (LR) HPV genital infection: Isolation of multiple types of LR-HPV DNA from a genital specimen using a validated / QC testing system

Multiple mixed high and low risk HPV genital infection: Isolation of multiple types of HR and LR-HPV DNA from a genital specimen using a validated / QC testing system

Vaccine-type associated mild, moderate, severe dyskaryosis, severe dyskaryosis/invasive, glandular abnormality, adenocarcinoma, other: Clinically diagnosed cases that have had vaccine-type HPV DNA isolated from the associated LBC specimen, with or without other HPV-type DNA.

Non-vaccine-type associated mild, moderate and severe dyskaryosis, severe dyskaryosis/invasive, glandular abnormality, adenocarcinoma, other: Clinically diagnosed cases that have had non-vaccine-type HPV DNA isolated from the associated LBC specimen, without other vaccine-type HPV DNA.

Possible vaccination failure: Identification of DNA for any vaccine-type HPV in at least one genital sample (by a validated/QC testing system) from a female

in a birth cohort targeted for HPV vaccination, with or without known history of vaccination, after end of relevant vaccine round.

Probable vaccination failure: Identification of DNA for any vaccine-type HPV in at least one genital sample (by a validated/QC testing system) from a female with a recorded history of complete vaccination (administered in accordance with manufacturer's recommendations).

Confirmed vaccine failures will not be monitored here. Monitoring of confirmed vaccine failures would, at present, only be possible with evidence that there was no pre-existing vaccine-type HPV infection. This information will not be available; however if detection methods are developed that allow identification of a confirmed vaccine failure, we will include this outcome in surveillance.

8.3.4: Sample sizes

- 2000 LBC specimens at baseline and 1000 per year thereafter

The sample size calculation is based upon the overall HPV prevalence, high-risk type HPV prevalence, prevalence of HPV types 16/18 and the need to monitor the emergence of rare subtypes (increase in prevalence of relatively rare HPV subtypes).

Among women under 25, 40% are HPV positive, 25% are high-risk HPV positive and 12% are HPV 16/18 positive (9% type-16 and 3% type-18). The latter percentages are based upon data from studies conducted in Lothian.

With these assumptions we anticipate that of the women in the catch-up campaign:

- 34% will be HPV positive at first cervical smear
- 19% will be HPV positive with a high-risk HPV type
- 7% will be HPV-16 or 18 positive.

With these assumptions, and provided 2000 LBC samples are collected pre-vaccination and 3000 post-vaccination over 3 years, we anticipate that by the time those in the catch-up campaign aged 15, 16, 17 in September 2008 come for their first cervical smear there will be at least a 99% power to detect

- A 15% reduction in HPV prevalence at first cervical screen from 40% to 34%
- A 25% reduction in HR-HPV prevalence at first cervical screen from 25% to 19%
- A 40% reduction in HPV 16/18 prevalence at first cervical screen from 12% to 7%

8.3.5: Dataset

Table 4: Minimum Dataset for Testing of LBC Specimens and Biopsies

Label	Format	Preferred Input	Description	Source of Data
Date of Specimen	Date	MM/YYYY	Patient Specimen / Screening Date	SCCRS
Age	Age	YY	Age at Screening	SCCRS
Deprivation Category	Numeric	NN	Scottish Index of Multiple Deprivation Category, derived from postcode data	SCCRS
Age at vaccination	Age	YY	Age at completed course of vaccine	CHSP-S
Date at last vaccination	Date	MM/YYYY	Patient vaccination date for last administered course	CHSP-S
Vaccination Status	Numeric	N	0 = unvaccinated 1 = incomplete course – 1 dose 2 = incomplete course – 2 doses 3 = fully vaccinated, completed course 4 = Status unknown	CHSP-S
Cytology Results (most severe result per individual per year only)	Numeric	N	*Cytology results* 0 = Normal smear 1 = unsatisfactory smear 2 = borderline smear 3 = mild dyskaryosis 4 = moderate dyskaryosis 5 = severe dyskaryosis 6 = severe dyskaryosis / invasive 7 = glandular abnormality 8 = Adenocarcinoma 9 = Other	SCCRS
Pathology / Biopsy Results	Numeric	N	*Pathology / Biopsy Results*: 0 = none 1= CIN 1 2 = CIN 2 3 = CIN 3 4 = CGIN 5 = invasive squamous carcinoma 5 = adenocarcinoma 6 = cancer of the cervix uteri 7 = other	SCCRS
HPV Status	Binary Numeric	N	0 = Negative 1 = Positive 2 = insufficient	NHPVRL

Type specific HPV	Binary Numeric	N	0 = No 1 = Yes	NHPVRL
Other unrecognised / undefined type	Binary Numeric	N	0 = No 1 = Yes	NHPVRL

(Type specific HPV type: Types 16, 18, 6, 11, 31, 33, 40, 45, 51, 53, 54, 58, 59, 66, 68, 70 and other types yet to be decided)

8.3.6: Data Analysis and Outputs

We will compare baseline and post-vaccination levels of HPV prevalence in women coming forward for screening in order to determine if the vaccine programme is associated with a reduction in the prevalence of HPV-16 and 18 over time. This is one of the main tests of the effect of the vaccination programme. It will also allow us to ascertain if there are any increases in non-vaccine types due to type replacement or any decreases in non-vaccine types due to cross-protection.

Implicit in this analysis is the absence of a systematic bias associated with the types of women coming for screening. If over time, there is an impact of the vaccination programme such that women who are vaccinated are less likely to come for screening then we may see no reduction in the HPV16/18 prevalence in the screening samples. This bias can be assessed through the linked SCCRS - CHSP-S dataset outlined above to estimate the extent to which being vaccinated changes the propensity to come for screening.

HPV prevalence and type-specific prevalence will be estimated using confidence intervals for binomial proportions. For rarer types exact binomial methods will be used. Changes in prevalence will be assessed using tests on proportions and logistic regression. Again for rarer sub-types exact logistic regression and exact tests will be used.

Table 5: Data analysis outputs for testing of LBC specimens from women attending routine cervical screening

	HPV Positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	HPV 16/18/ vaccine type/ non-vaccine type/ high-risk type/ low-risk type/ multiple type etc.etc genital infection positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	Vaccine-type dyskaryosis / glandular abnormality / adenocarcinoma positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	Non-vaccine-type dyskaryosis / glandular abnormality /adenocarcinoma positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						

	Possible / probable vaccine failure for genital infection positive	Total	Prevalence Rate %	Relative Risk	Unadjusted odds ratio, 95%CI	Adjusted odds ratio, 95%CI
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						

Note: A separate output will be produced for each type-specific HPV infection, for each category of infection, lesion and cancer and for each explanatory variable; these are aggregated here for the purposes of brevity.

8.4.0: Surveillance of the type-specific prevalence of cervical intraepithelial neoplasia (CIN) 2, 3, CGIN, Cancer of the Cervix, Invasive Squamous Cell Carcinoma and Adenocarcinoma.

Depending on the numbers involved, it is proposed that all or a sample of CIN 2s and 3s, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma in individuals aged 20 to 24 years of age should be typed for HPV to determine the proportion of cervical lesions associated with vaccine and non-vaccine types. Typing of biopsy blocks will be conducted every second year. We will preferentially sample biopsies from those aged 20 to 21 and biopsies associated with CIN3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma. This will allow us to identify break-through infections in vaccinated individuals.

8.4.1: Objectives

To monitor the HPV-types associated with pre-cancerous cervical lesions and invasive cervical cancer (CIN 2 and 3, CGIN, cancer of the cervix uteri, invasive squamous cell carcinoma and adenocarcinoma) in birth cohorts offered the vaccine.

8.4.2: Methods

Methods will be for section 8.1 above, with the addition of HPV typing results for CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma. We will identify those diagnosed with these endpoints from the HPV surveillance system and we will select a random sample for HPV testing and typing. We will assign an anonymous study number to each individual. We will contact the histopathology lab that made the diagnosis and we will ask them to submit a sample, from the biopsy block associated with an individual's most severe diagnosis, to the SNHPVRL. The SNHPVRL will report results to HPS. We will collect an additional 10% of specimens on top of that needed for our calculations to compensate for samples from which HPV cannot be extracted. Histopathology labs will be approached in the first instance to participate in surveillance through the Scottish Pathology Network.

8.4.2: Baseline survey / Pilot

Baseline specimens and data will be collected in a pilot survey from non-vaccinated cohorts attending for their first smear in the one or two years prior to the first vaccinated cohort entering the screening programme.

8.4.3: Case Definitions

Vaccine-type associated CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma: Clinically diagnosed cases that have had vaccine-type HPV DNA isolated from biopsy tissue with or without other HPV-type DNA.

Non-vaccine-type associated CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma: Clinically diagnosed cases that have had non-vaccine-type HPV DNA isolated from biopsy tissue without other vaccine-type HPV DNA.

CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma of undetermined cause: Clinically diagnosed cases without identification of HPV DNA after testing with a validated/QC testing system.

Possible vaccine failure for cervical disease: Diagnosis of vaccine-type related CIN2+ / CGIN+ in a female in a birth cohort targeted for HPV vaccination, without a recorded history of complete vaccination, X1 months (CIN1), X2 months (CIN2), X3 months (CIN3/CGIN) or X4 years (invasive cancers) or more after end of relevant vaccine round.

Probable vaccine failure for cervical disease: Diagnosis of vaccine-type related CIN2+ / CGIN+ in a female with a recorded history of complete vaccination (administered in accordance with manufacturer's recommendations), Y1 months (CIN1), Y2 months (CIN2), Y3 months (CIN3/CGIN) or Y4 years (invasive cancers) or more after completion of vaccine course.

We will collaborate with HPA to determine appropriate values for X1-4 and Y1-4. These will be decided and tested during the first year of the surveillance programme. Investigation of vaccine failures will be the subject of a separate protocol and will be subject to ethical approval.

8.4.4: Sample sizes for monitoring of type-specific prevalence of CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma

- 500 biopsies at baseline and 500 every second year thereafter

At present 60% of high-grade abnormalities are associated with HPV16/18. Vaccination is anticipated to result in a 50% reduction in CIN2/3 prevalence in the catch-up birth-cohorts and an 86% reduction in CIN2/3 prevalence in birth-

cohorts vaccinated as part of the core immunisation programme. Smaller reductions must be anticipated in the early years while those in the catch-up campaign come through for screening.

This sample size will confer a 96% power to detect a 20% reduction from 60% to 48% in the percentage of CIN2/3 associated with HPV-16/18.

8.4.5: Dataset

The dataset will be as for section 8.3 above.

8.4.6: Data Analysis & Outputs

HPV prevalence and type-specific prevalence will be estimated using confidence intervals for binomial proportions. In some cases for rarer types, exact binomial methods will be used. Changes in prevalence will be assessed using tests on proportions and logistic regression. Again for rarer sub-types exact logistic regression and exact tests will be used.

Ideally the 500 biopsies selected should be a random sample of all cases detected. We will preferentially sample cancers, CIN3 and CGIN. We will sample preferentially from women aged 20 to 21 years, although it is likely that given the low prevalence of high-grade pre-cancerous lesions in women of this age, that we may need to sample from women aged 20 to 24 years. By extracting relevant demographic data from SCCRS sample weights can be calculated to correct for any bias in the 500 women tested.

In reality we anticipate that the actual number of pre-cancerous lesions and cancers diagnosed in our surveillance population immunised as part of the routine programme will be less than 500 per year, in which case we may sample from over two-years to obtain the required sample size, with the analysis being conducted only every second year.

Table 6: Data analysis outputs for testing of CIN2/3 & cancers from women attending routine cervical screening

	Vaccine-type CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	Non-vaccine-type CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	CIN2/3, CGIN, cancer of the cervix, invasive squamous cell carcinoma and adenocarcinoma of undetermined cause positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	Possible vaccine failure for cervical disease positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at						

Immunisation						
Health Board						
	Probable vaccine failure for cervical disease positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						
	Confirmed vaccine failure for cervical disease positive	**Total**	**Prevalence Rate %**	**Relative Risk**	**Unadjusted odds ratio, 95%CI**	**Adjusted odds ratio, 95%CI**
Total						
Immunisation Status						
SIMD Category						
Age at Immunisation						
Health Board						

Note: A separate output will be produced for each grade of lesion / carcinoma and each explanatory variable; these are aggregated here for the purposes of brevity.

9.0: Surveillance of females who do not attend cervical screening.

It will be necessary to monitor the characteristics of those who decline to attend screening, our hard-to-reach population, to define them in terms of their vaccination status and in terms of their demographic characteristics. Age and post-code data for this population can be extracted from SCCRS. Post-code data will be used to characterise non-attendees according to their SIMD category and geographic location (health board of residence). As before, immunisation status will be ascertained through linkage with the CHSP-S database. This information will be used to define the overall characteristics of, and the representativeness of surveillance activities targeted at, this population.

Two options for surveillance of the hard-to-reach population are outlined here using either a direct survey or by testing of readily available specimens. Each survey will require the development of a full and detailed protocol that will address issues of the bias, response and the ethics associated with the approach. These issues are beyond the scope of this protocol. This survey will be conducted every second year.

9.1: Determining HPV prevalence and type-specific prevalence in non-attendees at cervical screening by postal survey– preferred option.

A postal survey of a representative sample of non-attendees at screening will be conducted every two years to monitor the type-specific prevalence of HPV. Potential participants will be identified from SCCRS and will be sent a kit and asked to return an anonymous self-collected specimen for testing for HPV. As we expect the response to the survey to be very low, the number of individuals that we will need to contact will need to be at least ten times that of the required sample size. A full protocol for this survey will be worked out and will be subject to approval from the National Ethics Committee for Scotland. The first year of this survey will act as a pilot and the exact methodology will be refined on the basis of the outcome of this. This approach may be subject to considerable response bias, although it will have the advantage of being a direct survey of the 40% of our population who default on screening. As we will know the characteristics of this population, we will be able to describe any bias associated with poor response.

9.2: Secondary testing of residual Chlamydia specimens.

It is proposed that samples submitted for Chlamydia testing would provide a suitable source of specimens for screening for HPV. There is no routine organised Chlamydia screening service in Scotland. Screening is opportunistic through GP practices and GUM clinics. Many of those who submit specimens do so because they perceive themselves to be at high risk of infection, indicating that this population is more likely to engage in high-risk sexual behaviour than the general population. This population is likely to be at higher risk of HPV infection and therefore represent a biased population. In order to control for this bias, a baseline survey in this population would need to be conducted. The results of this survey could then be adjusted using the results on HPV prevalence in the general population from the national prevalence survey and data from other surveys on sexual behaviour in the general population, such as the National Survey of Sexual Attitudes and Lifestyles.

Currently there is no demographic data available on those submitting specimens through home testing kits. Specimens submitted through GP practices are often accompanied by limited data. The most well characterised population submitting specimens are those who present for testing through GUM services. Data on the characteristics of those submitting Chlamydia specimens would need to be collected to ensure the characteristics of this population are understood. As Chlamydia testing becomes increasingly routine in Scotland, particularly through the use of home-testing kits and testing through GP practices, the characteristics of those presenting for screening may change. The characteristics of those who present for screening through GUM services may be more stable.

GUM attendees may include a large proportion of our hard-to-reach population. For these reasons it is proposed that HPV testing of Chlamydia

specimens should primarily focus on specimens submitted through GUM clinics.

Either urinary samples or genital swabs are submitted for Chlamydia testing and either of these would be suitable for HPV testing. Specimens are submitted to 15 laboratories across Scotland and a number of these could be selected as sentinel laboratories for surveillance. Only specimens submitted by females would be selected, although this could in future be extended to males. An aliquot of specimens submitted for Chlamydia testing could be taken at the laboratory and forwarded to the SNHPVRL for HPV screening and typing.

We could organise surveillance of this population in either of two ways:

a. Specimen collection through Chlamydia screening laboratories and extraction of data from NaSH using one way encryption

b. Unlinked anonymous secondary testing of residual Chlamydia specimens organised through GUM clinics

The advantage of this approach is that we have a readily available source of specimens. The main disadvantage is that the population will be biased towards those most at risk of infection and they will not be representative of the general population. We may be able to control for this somewhat by comparing baseline prevalence rates in this population to that in our national prevalence survey.

9.3: Case Definitions

Case definitions for HPV-16 and -18 infections, for high-risk, low-risk, vaccine-type, non-vaccine type, multiple high-risk type, multiple low-risk type and multiple mixed high and low-risk type HPV genital infection will be as for section 8.2 above.

9.4: Sample size

The sample size calculation is only carried out for the preferred option of a random sample of unscreened women via a postal survey and self taken sample. We propose to recruit random samples of 1000 women at baseline pre-vaccination and 2000 women every 2 years post-vaccination. These samples will be compared with the samples of screened women selected at the same time points.

No major differences in HPV positivity are anticipated between the screened and unscreened women at baseline, but there is a possibility that HPV positivity may be greater in the unscreened group. With 2000 women in the baseline survey of screened women and 1000 in the baseline survey of unscreened women there is a 90% power to detect differences in HPV positivity of around ± 6% points, i.e. from 40% to 34%, or from 43% to 37%.

Among vaccinated cohorts, 2000 unscreened women will be surveyed every second year and the LBC specimens of 2000 women attending for screening will also be surveyed. During the vaccination campaign we anticipate that HPV prevalence will decrease in both groups and there will be at least a 90% power to detect differences of ± 5% points between the two groups.

This means that a direct comparison of the vaccine effect can be made by comparing HPV prevalence in women who are vaccinated with those unvaccinated, in screened and unscreened women. This is not a randomised comparison, so there may be selection bias, but there will be approximately 1600 vaccinated women and 2400 unvaccinated, giving powers in excess of 90% to detect reductions of 15% in HPV positivity and reductions of 30% in HPV 16/18 positivity.

10.0: Surveillance of Males

Determining overall and type-specific HPV prevalence in males

To assess the extent of herd immunity in males achieved by immunising females, it is proposed that the feasibility of carrying out a study based on testing a sample of boys in the cohorts now aged 11 to 18 years participating in the baseline prevalence study, be examined.

Our sample could come from a number of sources:

- A repeat survey of males in secondary education and further education colleges could be undertaken using the same methodology as that employed by the baseline prevalence survey
- A sentinel survey of males could be undertaken. We could recruit participants from a variety of sources such as community health hubs or those attending GUM clinics
- Secondary testing of Chlamydia specimens submitted by males, in line with that proposed for females.

This aspect of surveillance will not be addressed in this protocol. It will be the subject of a future proposal.

11.0: Determining Vaccine Effectiveness

HPS will collaborate with the HPA in the UK programme to determine the effectiveness of the vaccination programme in Scotland. Vaccine effectiveness (VE) is the percentage reduction in disease incidence attributable to vaccination [5]. It is calculated using the formula:

$1 – (ARV/ARU) \times 100$

Where ARV = attack rate in the vaccinated and ARU = attack rate in the unvaccinated.

VE will be assessed by both the cohort method, also known as the Broome method [6] (which compares the proportion of vaccine and non-vaccine types isolated from immunised and non-immunised cases) and the screening method [7] (which requires information on the proportion of cases vaccinated compared with the proportion of the population in that age group vaccinated). VE will be determined in both the population of women attending for cervical screening as well as in women who default on cervical screening and these estimates will be combined to give an estimate in the population as a whole.

11.1: The Cohort Method.

This method uses the number of cases in the vaccinated and the unvaccinated to determine vaccine effectiveness using the formula:

VE = 1 – a.N2/cN1

a = number of cases in the vaccinated due to the vaccine type
N1 = total number of vaccinated
c = number of cases in unvaccinated due to vaccine type
N2 = total number unvaccinated

If we assume that the risk of non-vaccine type infections remains the same in the vaccinated population as in the unvaccinated population then VE can be estimated as:

VE = 1 – ad/bc

Where
a = number of cases in the vaccinated due to the vaccine type
b = number of cases in the vaccinated due to non-vaccine types
c = number of cases in unvaccinated due to vaccine type
d = number of cases in unvaccinated due to non-vaccine types.

It is possible that the proportion of vaccine-type disease in unvaccinated populations may decrease due to the effects of herd immunity in which case we will overestimate VE or that the proportion of non-vaccine type disease may increase due to type replacement, in which case this method may result in an underestimation of VE.

This method may be used to estimate effectiveness in high risk groups and to investigate whether this differs from other groups.

11.2: The Screening Method:

This method involves comparing the proportion of cases vaccinated compared to the proportion of the population in that age-group that is vaccinated. Data from CHSP-S on vaccine coverage in the overall population will be applied to facilitate external standardisation of these calculations. This will enable the calculation of confidence intervals and the control of confounding. A number of covariates will be included in the analysis including age at vaccination, birth cohort, SIMD and health board of immunisation.

VE will be determined using the formula:

$$VE = \frac{PPV\text{-}PCV}{PPV(1\text{-}PCV)}$$

Where PPV = proportion of the population vaccinated and PCV = proportion of cases vaccinated. The relative risk of disease can then be calculated (1-VE) and this is equal to the odds ratio of vaccination in cases and the population.

11.3: Confounding Factors:

Estimates of VE are likely to be confounded by selection bias in our cervical screening population and in surveys of the unscreened population. It is not known whether the HPV vaccination programme will have an impact on attendance at cervical screening and on the characteristics of those who attend for screening. At present we know that attendance at screening decreases with increasing social deprivation and that the risk of HPV related disease increases with social deprivation [3, 4]. If this remains unchanged among vaccinated birth-cohorts then estimates of VE in those attending cervical screenign are likely to be an overestimate.

We recognise that both proposed approaches to monitoring the unscreened population are subject to bias. We expect a low response rate to the proposed postal survey and we expect that those who are at the highest risk of HPV infection are less likely to respond to the survey. Therefore measures of VE from this survey will be an overestimate. This approach has the advantage of being a population based survey however and we will be able to fully characterise any response bias using demographic and SIMD data derived from SCCRS.

Using a convenience sample of those submitting Chlamydia specimens through GUM clinics will capture a population whose sexual health is poor and who are at high-risk of infection. Measures of VE from this population may be an underestimate of VE in the unscreened population.

We will attempt to adjust for these confounding factors by including indicators associated with HPV related disease such as social deprivation and age at immunisation in our multivariable model.

12.0: Full Statistical Analysis Plan

The full analysis plan for all surveillance activities are presented here.

A. Surveillance of the incidence and prevalence of abnormal smears and cervical abnormalities and type specific prevalence of cervical intraepithelial neoplasia (CIN) 2, 3.

- 500 CIN2/3 at baseline and 500 every second year thereafter

HPV prevalence, and type specific prevalence, will be estimated using confidence intervals for binomial proportions. In some cases for rarer types exact binomial methods will be used. Changes in prevalence will be assessed using tests on proportions and logistic regression. Again for rarer sub types exact logistic regression and exact tests will be used.

Logistic regression will also be used to assess the impact of vaccination on HPV type prevalence.

Ideally the 500 CIN2/3 selected should be a random sample of all CIN2/3 cases detected. By extracting relevant data from SCCRS sample weights can be calculated to correct for any bias in the 500 women tested.

B. Determining overall and type-specific HPV prevalence in a representative sample of females from cohorts who have been invited for HPV immunisation and who are attending for their first cervical screening appointments.

At baseline (pre vaccination) there are two study groups – 2000 women aged 20 coming for cervical screening (denoted S-B) and 1000 women aged 21 who did not attend their cervical screen (denoted NS-B). Post vaccination there are 1000 women per year selected at random from all women coming for screening (S-Y1, S-Y2, etc where the number denotes the year) and a random sample of 2000 women every second year who did not attend screening (NS-Y2, etc). Women in the NS-Y2 sample are from the same birth cohort as the S-Y1 sample but will be one year older on recruitment. Within the S-Yi samples and the NS-Yi samples there will be both vaccinated and unvaccinated women, denoted S-Yi-V and S-Yi-NV, for example. We anticipate that about 40% of women aged 20 will be vaccinated by the second year post vaccination.

Note that this assumption of 40% of women aged 20 will be vaccinated depends upon the Phase IV study (described on page 13) going ahead. If it does not then the post vaccination data collection will need to be postponed until women age under 18 on Sept 1 2008 come forward for screening. In this case we also estimate that 40% of the age group will be vaccinated but if the catch up campaign is more successful then this figure will increase. All of the statistical analysis will be carried out using logistic regression, reporting disease prevalence and confidence intervals.

A number of direct comparisons of HPV prevalence, both overall and subtype specific, can be carried out within this surveillance system. In all of these only

the data sets collected over the baseline and years 1 and 1 post vaccination are mentioned. However it is anticipated that data will be collected in years 3, 4 and so on. This will naturally be included in the analysis for the investigation of trends.

1. Comparison of screened and unscreened women at baseline (S-B and NS-B).

> Do unscreened women have different levels of HPV Prevalence from screened women?
>
> We have no direct evidence to expect this and in the absence of a significant difference these two samples can be pooled for comparison with the post vaccination samples to increase the power of the comparisons, pre and post vaccination.
>
> Implicit in this analysis is the absence of any systematic bias as a result of (a) the different method of collecting the samples in the screened (smear sample taken by nurse) and unscreened (self taken) or (b) age. Bias associated with a one year difference in age is not likely to be great. To an extent, age can be adjusted for in a statistical analysis if we know the age of the respondent and there is some overlap in the ages of women in the screened and unscreened samples.

2. Comparison of baseline and post vaccine levels of HPV prevalence in women coming forward for screening (S-B and S-Y1+S-Y2).

> Is the vaccine programme associated with a reduction in HPV prevalence in screened women?
>
> This is one of the main tests of the effect of the vaccination programme and we anticipate reductions in HPV16/18 prevalence over time. There may be increases in non HPV16/18 types, and/or and overall reduction in HPV positivity.
>
> Implicit in this analysis is the absence of a systematic bias associated with the types of women coming for screening. If, over time, there is an impact of the vaccination programme such that women who are vaccinated are less likely to come for screening then we may see no reduction in the HPV16/18 prevalence in the screening samples. This bias can be estimated by linking SIRS to SCCRS to estimate the extent to which being vaccinated changes the propensity to come for screening.

3. Comparison of baseline and post vaccine levels of HPV prevalence in women not coming forward for screening (NS-B and NS-Y2).

> Is the vaccine programme associated with a reduction in HPV prevalence in unscreened women?

4. Comparison of post vaccination levels of HPV prevalence in screened and unscreened women (S-Y1+S-Y2 and NS-Y2).

> Do unscreened women have different levels of HPV prevalence from screened women post vaccination?

We have no direct evidence to expect this. We have no reason to expect different levels of vaccine uptake in the two groups of women, though there may be. In the absence of a significant difference these two samples can be pooled for comparison with the post vaccination samples to increase the power of the comparisons, pre and post vaccination.

Again this comparison has the same caveats as 1 with regard to possible biases

5. Comparison of the differences in HPV prevalence between screened and unscreened women at baseline and post vaccine (S-B versus NS-B and S-Y1+S-Y2 versus NS-Y2).

This is an interaction test and is only included to make sure that it is reasonable to pool the data for 6 below. In the absence of an interaction pooling is appropriate.

We do not foresee any mechanistic reason that the effects of the vaccination programme should be different in the screened and unscreened women. There may be selection biases influencing women in their decision as to go for screening or not which may have an impact.

Again this comparison has the same caveats as 1 with regard to possible biases as regards the way the smear samples are taken.

6. Comparison of baseline and post vaccine levels of HPV prevalence in women in Scotland (S-B + NS-B and S-Y1+S-Y2+NS-Y2).

In the absence of major differences in HPV prevalence between the screened and unscreened women the two data sets can be combined and there are then 3000 samples at baseline and 4000 post vaccination. This provides much greater power for the detection of changes in HPV prevalence than in the screened and unscreened sub populations.

Furthermore pooling the screened and unscreened sample provides a stratified random sample of the whole female population of Scotland and so we have a national estimate of the vaccination programme. The analysis needs to take into account the relevant sampling weights as the sampling fractions in the screened and unscreened sub populations are not identical.

7. Comparison of the levels of HPV prevalence in the vaccinated and unvaccinated women (S-Y1-V+S-Y2-V+NS-Y2-V and S-Y1-NV+S-Y2-NV+NS-Y2-NV).

Do vaccinated women have lower levels of HPV prevalence from unvaccinated women post vaccination?

This is the comparison which is closest to the comparisons within a randomised clinical trial though there is no randomisation here. (Note that is the proposed Phase IV study goes ahead then there will be a randomised comparison in year 1 but this will have low power).

From this analysis we will also be able to estimate Vaccine Effect. By linking the data on the sampled women (2000 in S-Y1and S-Y2 and 2000 in NS-Y2) to CHSP-S the vaccine status will be known, in terms of date of vaccination and number of courses. The odds ratio of HPV 16/18 positivity can be calculated and hence the vaccine effect estimated.

This analysis has the same caveats as 1 and if it transpires that there are differences in HPV positivity associated with the ways the smear samples are taken then a stratified analysis will be carried out here, adjusting for the sub population the women comes from (screening or non screening).

13.0: Data Linkage and Processing

Data will be extracted, linked and collated at ISD; an anonymised dataset will be analysed and stored at HPS. Data that pertains to the previous year will be extracted and linked so there will be over a one year delay in the reporting of results from the system. This will allow for women to go through three rounds of invitations to screening before being defined as defaulters and to allow for the reporting of pathology results onto SCCRS.

13.1: Data Processing and Analysis

The linked screening and immunisation dataset will be transferred electronically to HPS from ISD. This will include a link to the anonymised study ID attached to residual LBC samples. HPV test results from the NHPVRL which include the anonymised study ID will also be sent to HPS electronically. The full surveillance dataset will be cleaned, stored and analysed at HPS. Data will be stored in secure password protected SQL databases. Statistical analysis will be done using SPSS® 14.0 for Windows, STATA, S-Plus and R at HPS in accordance with the Data Protection Act.

An information officer will be employed to manage the database. Data will be checked for duplicate entries, for consistency and for accuracy.

14.0: Limitations

This system will be subject to a number of limitations such as selection bias associated with each arm of the surveillance system as previously discussed as well as inaccuracy of the data held on SCCRS and CHSP-S.

Both SCCRS and CHSP-S represent shifting populations. It is likely that some of those recorded on CHSP-S will no longer be resident in Scotland. SCCRS will include records for women immunised outside of Scotland, for women no longer resident in Scotland and also for women who were never resident in Scotland but who attained a CHI number through contact with the health service while visiting the country. This will lead to overestimates of our denominator from both of these databases. We will attempt to correct for this by comparing to other sources of population data such as birth and death registers.

Furthermore for some of those that are still resident in Scotland and eligible for screening, their demographic data as recorded on SCCRS are no longer accurate and this may impact on the validity of characterising our population by for instance social deprivation or by health board of residence. Again we will compare our data to other existing sources of data to assess the validity of our data.

15.0: Quality Assurance

We will undertake an in-depth and thorough evaluation of this system, at a future time as yet to be determined. This will be the subject of a separate evaluation project. We will evaluate the system in relation to the following attributes:

Timeliness
Data Quality
Simplicity
Flexibility
Stability
Usefulness
Acceptability
Sensitivity/Specificity
Predictive value positive
Cost-effectiveness

Appropriate ethical approval will be sought prior to the instigation of the various arms of the surveillance system. Elements of the surveillance system will be subject to the approval of the HPS Clinical Governance Committee; the ISD privacy advisory committee and the national research ethics approval process. All data will be collected, stored and analysed in accordance with the Data Protection Act and Caldicott Guidelines.

16.0: Pilot

Baseline surveys will be conducted using the same methodology as the core surveillance system and will therefore act as a pilot for the system. The pilot will be used to evaluate the surveillance system using those attributes specified in section 15.0. Necessary changes to design and running of the system will be made based on the outcome of the pilot.

17.0: Outputs

Results will be published in quarterly and annual reports and other suitable forms of public communications as yet to be decided. These reports will provide data on the overall and type specific HPV prevalence amongst females reporting for their first cervical smear and will also detail the results of sentinel surveillance of hard-to-reach groups. Reports will be disseminated to the appropriate stakeholders including: the Scottish Cervical Screening Programme, the Scottish Government, relevant public health authorities, primary care, front-line clinicians and health-care practitioners and the public.

The programme will produce outputs on:

- Trends in the type-specific prevalence of HPV in the Scottish population, particularly in hard-to-reach groups,
- Association between vaccination status and overall and type-specific HPV prevalence in females,
- Association between overall and type-specific HPV prevalence with age, and social deprivation,
- An assessment of the impact of the vaccination programme on the prevalence of vaccine and non-vaccine genotypes in females,
- Instances of breakthrough infections associated with vaccination,

Data from the surveillance system will be fed into an overall evaluation of the immunisation programme. The results of this evaluation will be reported to the Scottish Government Health Department, the Department of Health, the JCVI, the Health Protection Agency, the cervical screening service, immunisation co-ordinators, Directors of Public Health and front-line clinicians and healthcare practitioners.

Data will be presented at appropriate national and international scientific meetings and conferences. Data from the surveillance system will be published in national and international surveillance and epidemiological bulletins and in peer-reviewed scientific journals.

18.0: Stakeholders

The key stakeholders have so far been identified as:

Scottish Government Health Department (SGHD)
Health Protection Scotland (HPS)
Scottish National HPV Reference Laboratory (SNHPVRL)
Information Services Division (ISD)
National Services Division (NSD)
Clinical Virologists
Scottish Cervical Screening Service
Cytologists and cytopathologists
Colposcopists
Gynaecologists
Primary Care Health Practitioners
GUM physicians and frontline clinicians with an interest in sexual and reproductive health
Immunisation co-ordinators
Directors of Public Health (DPH) and Consultants in Public Health Medicine (CPHM)
The Joint Committee on Vaccination and Immunisation
Department of Health

Health Protection Agency
School Health Service
The public

An epidemiology and surveillance subgroup has been convened to advise on the development of the surveillance system. This group comprises representatives of the SGHD, HPS, NHPVRL, cytology and cytopathology, cervical screening, immunisation co-ordinators, consultants in public health, primary care and ISD. Further consultation with stakeholders is conducted through the HPV Immunisation Core Implementation Group, including DPHs and CPHMs, immunisation co-ordinators, the school health service and education.

19.0: Resources

Funding for the surveillance system will come from the HPS Surveillance Budget.

19.1: Estimated costs

Table 7: Projected surveillance costs, 2008 to 2012.

Baseline Costs	**2008/2009 (Half a Year)**	**2010/2011**	**2011/2012**
Core costs	£82,898	£184,356	£189,233
Total Surveillance Costs	£149,670	£289,878	£286,189
Subtotal Core & Surveillance	£232,568	£474,234	£475,422
Additional Set-up costs			
Non Recurring Revenue	£1000		
Capital Funding		£70,000	
Non Recurring Revenue	£3000		
Capital Funding	£45000		
Total Funding Required	***2008/2009***	***2010/2011***	***2011/2012***
Revenue	£236,568	£474,234	£475,422
Capital	£45,000	£70,000	
Total			**£1,301,224**

It is likely that there may be a need in future to expand surveillance activities to address additional aspects of the evaluation of the immunisation programme, such as investigation of vaccine failures. When the details of this additional surveillance are determined, additional funds will be sought.

20.0: References

1. ECDC 6 Nov. 2007. Guidance for the Introduction of HPV Vaccines in EU Countries, Stockholm, January 2008. Available from: http://ecdc.europa.eu/pdf/HPV_report.pdf. Accessed January 2008.

2. Kitchener, HC, Almonte, M, Wheeler, P, Desai, M, Gilham, C, Bailey, A. et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. British Jnl Cancer 2006; 95: 56 – 61.

3. Information Services Division, Information and Statistics. Cervical Screening Statistics. Available from: http://www.isdscotland.org/isd/1673.html. Accessed November 2007.

4. NHS Greater Glasgow Cervical Screening Programme Annual Report: April 2005 – March 2006. Board Paper No. 06/77, 19 December 2006. Available from: http://www.nhsggc.org.uk/content/ . Accessed March 2008.

5. Rivest, P and Allard, R. The effectiveness of serogroup C meningococcal vaccine estimated from routine surveillance data. Vaccine, 2002; 20: 2533 – 2536.

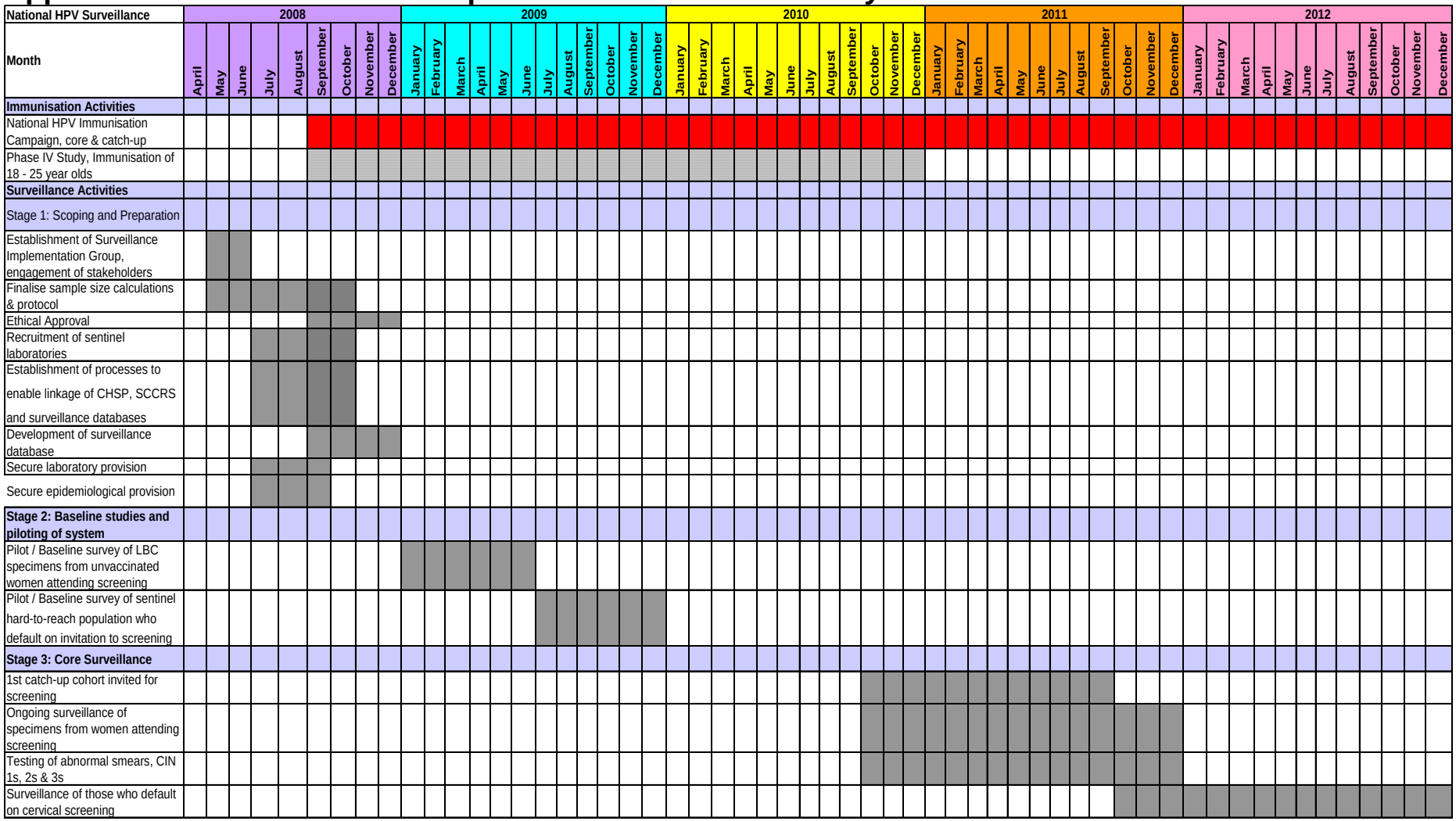
6. Broome, CV, Facklam, RR and Fraser DW. Pneumococcal Disease after Pneumococcal Vaccination. NEJM, 1980; 303; 10: 549 – 552.

7. Farrington, CP. Estimation of Vaccine Effectiveness Using the Screening Method. International Journal of Epidemiology 1993; 22 (4): 742 – 746.

8. Rambout, L, Hopkins, L, Hutton, B. and Fergusson, D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ* 2007;177 (5):469-79.

9. Cuschieri, KS, Cubie, HA, Whitley, MW, Seagar AL, Arends, MJ, Moore, C, et al. Multiple High Risk HPV Infections are common in cervical neoplasia and young women in a cervical screening population. J. Clin Pathol 2004; 57: 68 – 72.

Appendix 1: Timetable for Development of HPV Surveillance System



Appendix 2: Sample Sizes and Associated Costs

Typing of CIN2/3 to answer the following surveillance question:

What is the impact of the national HPV immunisation programme on the type-specific prevalence of CIN2/3 in 20 to 24 year olds?

At present 60% of high grade abnormalities are associated with HPV16/18. Vaccination is associated with a 50% reduction in CIN2/3 prevalence based upon an intention to treat analysis. This reduction (or greater, as the per protocol analysis shows an 86% reduction in CIN2/3)) can only be expected to be seen once the routine vaccination cohorts come through for screening. Rather smaller reductions must be anticipated in the early years while those in the catch up campaign come through for screening.

We anticipate a reduction in the numbers of CIN2/3 lesions detected at first smear post vaccination. This will be as a result of a reduction in the CIN2/3 lesions associated with HPV16/18. As a consequence we must expect that the percentage of CIN2/3 lesions associated with non HPV 16/18 types must increase post vaccination. To detect an increase in CIN2/3 non HPV 16/18 types we must consider as a baseline all women coming for screening.

For operational reasons we are proposing to type at least 500 CIN2/3 lesions pre vaccination and 500 post and the comparison of the HPV16/18 percentages is a valid analysis. However for detecting an increase in non HPV16/18 types the sampling fractions of the 500 from all CIN2/3 pre vaccination and the 500 from all CIN2/3 post vaccination must be taken into account in the analysis.

An alternative strategy would be to randomly select and type about 50% of all CIN2/3 lesions pre vaccination and post. This would likely correspond to samples of 500 pre vaccination and 300 post, based upon anticipated reductions in CIN2/3 prevalence. The statistical analysis with this design is easier but there would be limited information on the different subtypes and so a larger sample post vaccination is preferred.

Selecting 500 high grade lesions before vaccination and 500 after has a 96% power to detect a 20% reduction from 60% to 48% in the percentage of CIN2/3 associated with HPV 16/18. With 300 samples pre and post vaccination the power is 85% for a 20% reduction in HPV 16/18 types. Samples of 300 are too low and those of 500 have sufficient power.

Reduction in HPV 16/18 types sensitivity analysis

Screening and typing of a random sample of LBC specimens to answer the following surveillance question:

What is the impact of the national HPV immunisation programme on the overall type-specific prevalence of HPV infection in 20 to 24 year olds attending for cervical screening?

The sample size calculation is based upon the overall HPV prevalence, high risk HPV type prevalence, HPV Types 16/18 prevalence and emergence of rare subtypes (increase in prevalence of relatively rare HPV subtypes.

The timing of the selection of the pre vaccination sample depends crucially on whether or not the GSK Safety Study goes ahead among women aged 18-25. If so the pre vaccination LBC specimens have to be selected before women are vaccinated. If not we have until those in the catch up campaign reach their first cervical smear. In the estimation of the sample sizes required the following assumptions are made.

Among women under 25, 40% are HPV positive, 25% are High Risk-HPV positive and 12% are HPV 16/18 positive (9% type-16 and 3% type-18). The latter percentages are based upon data from Lothian.

The vaccine is 100% effective against HPV16/18 among women naïve to HPV16/18 at vaccination

40% of the catch up cohort aged 17 is vaccinated before their first cervical smear rising about 10% per year to 80% vaccinated in the routine campaign of 12 year olds.

If the GSK study goes ahead 40% of women currently aged 18-19 are vaccinated before their first cervical smear

With these assumptions we anticipate that of the women in the catch up campaign:

- 34% will be HPV positive at first cervical smear
- 19% will be HPV positive with a high risk HPV type
- 7% will be HPV 16 or 18 positive.

With these assumptions, and provided 2000 LBC samples are collected pre vaccination and 3000 post vaccination, we anticipate that by the time those in the catch up campaign aged 15, 16, 17 in Sept 2008 come for their first cervical smear there will be at least a 99% power to detect

- A 20% reduction in HPV positivity at first cervical screen from 40% to 34%
- A 25% reduction in high risk HPV positivity at first cervical screen from 25% to 19%
- A 40% reduction in HPV 16/18 positivity at first cervical screen from 12% to 7%

The minimum sample sizes required to assess the impact of the vaccination campaign on HPV prevalence, and HPV type prevalence, is 2000 women pre vaccination and 3000 post vaccination. This can be accomplished by selecting, at random, 1000 women coming forward at age 20 for first cervical smear per year, if there is no GSK safety study. If there is a study then the initial sample should be collected this year. The 3000 post vaccination is best collected over a 3 year period to give some information on trend, but if required could be delayed until those in the catch up campaign come forward for cervical screening. More samples are required post vaccination to assess the possibly emergence of non 16/18 subtypes.

Obviously larger samples would have a greater power and so are preferable from a statistical point of view, but incur a greater cost. Smaller samples would not have sufficient power to detect the anticipated differences.

Sensitivity Analysis for HPV Positivity

P1	P2	Reduction	N1	N2	Power
40	38	5	1000	1000	15.0
40	36	10	1000	1000	45.3
40	34	15	1000	1000	79.4
40	32	20	1000	1000	96.2
40	38	5	2000	2000	25.4
40	36	10	2000	2000	74.1
40	34	15	2000	2000	97.6
40	32	20	2000	2000	100.0
40	38	5	2000	3000	29.6
40	36	10	2000	3000	81.5
40	34	15	2000	3000	99.1
40	32	20	2000	3000	100.0
40	38	5	3000	3000	35.5
40	36	10	3000	3000	89.1
40	34	15	3000	3000	99.8
40	32	20	3000	3000	100.0
40	38	5	5000	3000	42.6
40	36	10	5000	3000	94.6
40	34	15	5000	3000	100.0
40	32	20	5000	3000	100.0
40	38	5	5000	3000	42.6
40	36	10	5000	3000	94.6
40	34	15	5000	3000	100.0
40	32	20	5000	3000	100.0

P1 – Prevalence Pre Vaccination
P2 – Prevalence Post Vaccination
Reduction – percentage reduction from P1 to P2
N1 – Number of LBC Samples Pre Vaccination
N2 – Number of LBC Samples Post Vaccination
Power – Power to detect the differences from P1 to P2.

The table above shows that reductions of 5% have a low power of detection but that reduction of 10% and above have a reasonable power for sample sizes in excess of 2000 pre and post vaccination.

Sensitivity Analysis High Risk HPV Types

P1	P2	Reduction	N1	N2	Power
25	24	5	1000	1000	10.0
25	22	10	1000	1000	25.9
25	21	15	1000	1000	51.2
25	20	20	1000	1000	76.4
25	24	5	2000	2000	15.1
25	22	10	2000	2000	45.9
25	21	15	2000	2000	80.3
25	20	20	2000	2000	96.6
25	24	5	2000	3000	17.3
25	22	10	2000	3000	53.3
25	21	15	2000	3000	87.0
25	20	20	2000	3000	98.6
25	24	5	3000	3000	20.4
25	22	10	3000	3000	62.4
25	21	15	3000	3000	93.1
25	20	20	3000	3000	99.6
25	24	5	5000	3000	24.1
25	22	10	5000	3000	71.8
25	21	15	5000	3000	97.1
25	20	20	5000	3000	99.9
25	24	5	5000	3000	24.1
25	22	10	5000	3000	71.8
25	21	15	5000	3000	97.1
25	20	20	5000	3000	99.9

P1 – Prevalence Pre Vaccination
P2 – Prevalence Post Vaccination
Reduction – percentage reduction from P1 to P2
N1 – Number of LBC Samples Pre Vaccination
N2 – Number of LBC Samples Post Vaccination
Power – Power to detect the differences from P1 to P2.

The above table shows that samples of size 1000 are too small to have an adequate power. Samples of 2000 or more have at least an 80% power to detect a 15 or 20 percent reduction.

Sensitivity Analysis HPV 16/18 Types

P1	P2	Reduction	N1	N2	Power
12	11	10	1000	1000	13.5
12	10	20	1000	1000	40.9
12	8	30	1000	1000	75.8
12	7	40	1000	1000	95.4
12	6	50	1000	1000	99.7
12	11	10	2000	2000	22.3
12	10	20	2000	2000	68.6
12	8	30	2000	2000	96.4
12	7	40	2000	2000	99.9
12	6	50	2000	2000	100.0
12	11	10	2000	3000	26.2
12	10	20	2000	3000	76.8
12	8	30	2000	3000	98.5
12	7	40	2000	3000	100.0
12	6	50	2000	3000	100.0
12	11	10	3000	3000	31.0
12	10	20	3000	3000	85.0
12	8	30	3000	3000	99.6
12	7	40	3000	3000	100.0
12	6	50	3000	3000	100.0
12	11	10	5000	3000	36.8
12	10	20	5000	3000	91.7
12	8	30	5000	3000	99.9
12	7	40	5000	3000	100.0
12	6	50	5000	3000	100.0
12	11	10	5000	3000	36.8
12	10	20	5000	3000	91.7
12	8	30	5000	3000	99.9
12	7	40	5000	3000	100.0

P1 – Prevalence Pre Vaccination
P2 – Prevalence Post Vaccination
Reduction – percentage reduction from P1 to P2
N1 – Number of LBC Samples Pre Vaccination
N2 – Number of LBC Samples Post Vaccination
Power – Power to detect the differences from P1 to P2.

The above table shows that percentage reductions of at least 40% can be detected with any sample sizes considered.

Sensitivity analysis for emergence of rare subtypes

P1	P2	Increase	N1	N2	Power
5	6	20	1000	1000	16.5
5	7	40	1000	1000	46.9
5	8	60	1000	1000	77.7
5	9	80	1000	1000	93.9
5	10	100	1000	1000	98.9
5	6	20	2000	2000	28.4
5	7	40	2000	2000	75.9
5	8	60	2000	2000	97.1
5	9	80	2000	2000	99.9
5	10	100	2000	2000	100.0
5	6	20	2000	3000	32.3
5	7	40	2000	3000	82.7
5	8	60	2000	3000	98.8
5	9	80	2000	3000	100.0
5	10	100	2000	3000	100.0
5	6	20	3000	3000	39.7
5	7	40	3000	3000	90.4
5	8	60	3000	3000	99.7
5	9	80	3000	3000	100.0
5	10	100	3000	3000	100.0
5	6	20	5000	3000	48.4
5	7	40	5000	3000	95.5
5	8	60	5000	3000	99.9
5	9	80	5000	3000	100.0
5	10	100	5000	3000	100.0
5	6	20	5000	5000	59.2
5	7	40	5000	5000	98.8
5	8	60	5000	5000	100.0
5	9	80	5000	5000	100.0
5	10	100	5000	5000	100.0

P1	P2	Increase	N1	N2	Power
1	2	100	1000	1000	45.2
1	3	200	1000	1000	89.2
1	4	300	1000	1000	99.1
1	5	400	1000	1000	100.0
1	6	500	1000	1000	100.0
1	2	100	2000	2000	74.0
1	3	200	2000	2000	99.5
1	4	300	2000	2000	100.0
1	5	400	2000	2000	100.0
1	6	500	2000	2000	100.0
1	2	100	2000	3000	80.4
1	3	200	2000	3000	99.9
1	4	300	2000	3000	100.0
1	5	400	2000	3000	100.0
1	6	500	2000	3000	100.0
1	2	100	3000	3000	89.0
1	3	200	3000	3000	100.0
1	4	300	3000	3000	100.0
1	5	400	3000	3000	100.0
1	6	500	3000	3000	100.0
1	2	100	5000	3000	94.7
1	3	200	5000	3000	100.0
1	4	300	5000	3000	100.0
1	5	400	5000	3000	100.0

P1 – Prevalence Pre Vaccination
P2 – Prevalence Post Vaccination
Increase – percentage increase from P1 to P2
N1 – Number of LBC Samples Pre Vaccination
N2 – Number of LBC Samples Post Vaccination
Power – Power to detect the differences from P1 to P2.

These tables show the powers to detect increases in the prevalence of rare subtypes which may not be important at present. With 2000 specimens pre vaccination and 3000 post vaccination there is at least 80% power to detect increases of at least 40%. Although the powers are large here, especially for a subtype with a prevalence of 1%, only very large increases can be detected. Furthermore with rare events, few cases are anticipated and larger sample sizes are required to ensure that there is an adequate representation of the subtypes in the final sample.

Screening and typing of a random sample of self-taken specimens or Chlamydia specimens to answer the following surveillance question:

What is the impact of the national HPV immunisation programme on the overall type-specific prevalence of HPV infection in 20 to 24 year olds who do not attend for cervical screening?

The main comparison will be between the random sample of 1000 women per year who are sampled and HPV tested from the sample of specimens from women attending for cervical screening and the women in the group who do not come for screening and who are not vaccinated. In this latter group HPV prevalence should remain at 40%. In the former group, some of whom will be vaccinated, we expect HPV prevalence to decrease to about 34%. A random sample of 2000 women from the non screened non vaccinated group would be required to detect the anticipated differences. This might best be sampled with 1000 one year and a further 1000 in other years. Samples of size 1000 in total would have an adequate power to detect a 15% reduction.

We do not know the size of this group. There are about 30,000 women in a year group and 60% come for screening. It is likely that there will be a big overlap between the screened women and women vaccinated in the catch up campaign and if uptake of the vaccine among 17 and 18 year olds is 40-50% then a guess at the number of women in the unvaccinated unscreened at age 20 group is 10,000. It may not be realistic to expect a 20% response rate from a postal screening survey, but 10% over two years may be achievable

P1	P2	Reduction	N1	N2	Power
40	38	5	1000	1000	15.0
40	36	10	1000	1000	45.3
40	34	15	1000	1000	79.4
40	32	20	1000	1000	96.2
40	38	5	2000	2000	25.4
40	36	10	2000	2000	74.1
40	34	15	2000	2000	97.6
40	32	20	2000	2000	100.0
40	38	5	2000	1000	18.4
40	36	10	2000	1000	56.4
40	34	15	2000	1000	89.4
40	32	20	2000	1000	99.1
40	38	5	2000	3000	29.6
40	36	10	2000	3000	81.5
40	34	15	2000	3000	99.1
40	32	20	2000	3000	100.0

P1 – Prevalence Non Screened
P2 – Prevalence Screened Post Vaccination
Decrease – percentage decrease from P1 to P2
N1 – Number of Women not screened
N2 – Number of Women screened Post Vaccination
Power – Power to detect the differences from P1 to P2.

P1	P2	Reduction	N1	N2	Power
60	54	10	200	200	22.8
60	48	20	200	200	67.4
60	42	30	200	200	95.2
60	36	40	200	200	99.8
60	30	50	200	200	100.0
60	54	10	300	300	31.7
60	48	20	300	300	84.0
60	42	30	300	300	99.4
60	36	40	300	300	100.0
60	30	50	300	300	100.0
60	54	10	500	300	38.4
60	48	20	500	300	91.1
60	42	30	500	300	99.9
60	36	40	500	300	100.0
60	30	50	500	300	100.0
60	54	10	500	500	48.3
60	48	20	500	500	96.9
60	42	30	500	500	100.0
60	36	40	500	500	100.0
60	30	50	500	500	100.0
60	54	10	800	500	56.8
60	48	20	800	500	98.9
60	42	30	800	500	100.0
60	36	40	800	500	100.0
60	30	50	800	500	100.0

P1 – Prevalence Pre Vaccination
P2 – Prevalence Post Vaccination
Reduction – percentage reduction from P1 to P2
N1 – Number of CIN2/3 Samples Pre Vaccination
N2 – Number of CIN2/3 Samples Post Vaccination
Power – Power to detect the differences from P1 to P2.

The table above shows that reductions of 10% have a low power of detection but that reductions of 20% and above have a reasonable power for sample sizes in excess of 300 pre and post vaccination.

Appendix 3: Background Epidemiology

Epidemiology to Inform Sample Size Calculation

1. Protective Effect of the Vaccine

A systematic review of the randomised controlled trials [1] conducted during the development of both the bivalent and quadrivalent vaccines reported the following:

These results relate to women aged 15 to 25 years who received all 3 vaccine doses, who had no more than 6 lifetime sexual partners and who had no prior abnormal results from Pap screening (>90% of participants). The per-protocol analyses relate to women not previously infected with vaccine type HPV strains and who received all three doses of the vaccine.

Prophylactic HPV vaccination confers the following effect:

<u>High grade cervical lesions CIN2 or worse</u>: (FUTURE II trial & PATRICIA)

Per-protocol meta-analysis: pooled, overall Peto odds ratio = 0.14 (95CI: 0.09 – 0.21) = 86% reduction

Intention to treat meta-analysis: OR = 0.52 (95CI: 0.43 – 0.63) = 48% reduction

Mean duration of follow up = 47.7 months but a subsequent abstract reported continued vaccine efficacy up to 5.5 years.

<u>Any cervical lesions:</u>

(5 published trials including FUTURE I, Harper et al, Lancet 2006, Mao et al, Obstet Gynecol 2006, Paavonen et al, Lancet 2007, Villa et al, Br J Cancer, 2006 - references available upon request)

- defined as low grade lesions, high-grade lesions, carcinoma in situ and cancerous lesions

Per-protocol meta-analysis pooled Peto odds ration = 0.13 (95CI: 0.09 – 0.2) = 87% reduction

Intention to treat meta analysis pooled odds ratio = 0.36 (95CI = 0.29 – 0.45) = 64% reduction

<u>Persistent HPV infection:</u>

- reported as a 6 month outcome: Harper et al, Koutsky et al, Mao et al, PATRICIA, Villa et al

- reported as a 12 month outcome: Harper et al and PATRICIA

At 6 months:
Per-protocol analysis – pooled OR = 0.14 (95CI = 0.11 – 0.19)
Modified intention-to-treat analysis: 0.22 (95CI: 0.18 – 0.27)

At 12 months:
Per-protocol analysis – pooled OR = 0.12 (95CI = 0.03 – 0.46) = 88% reduction
Modified intention-to-treat analysis: 0.26 (95CI: 0.16 – 0.41) = 74% reduction

Per-protocol analyses provide estimates of the effect in those who have not been exposed to HPV and who are fully compliant with the vaccine schedule. These can be used to estimate reductions in the core immunisation programme.

Modified intention-to-treat analyses provide estimates for heterogeneous populations that may be less compliant with the vaccine schedule and who may have been exposed to HPV prior to completion of the 3 dose schedule. These are the preferred estimates to be used in sample size calculations for the catch-up campaign.

These trials may be subject to a degree of participation bias. Those women who were recruited to the trial, predominantly white, healthy and were recruited mostly from third level education. They may not be representative of the general population.

Epidemiology of HPV related disease in the cervical screening population.

CIN1, 2 & 3

Table 1: Numbers of New Diagnoses of CIN 1 – 3 in 20 to 24 year olds by reporting laboratory / NHS Board, Scotland, 2007.

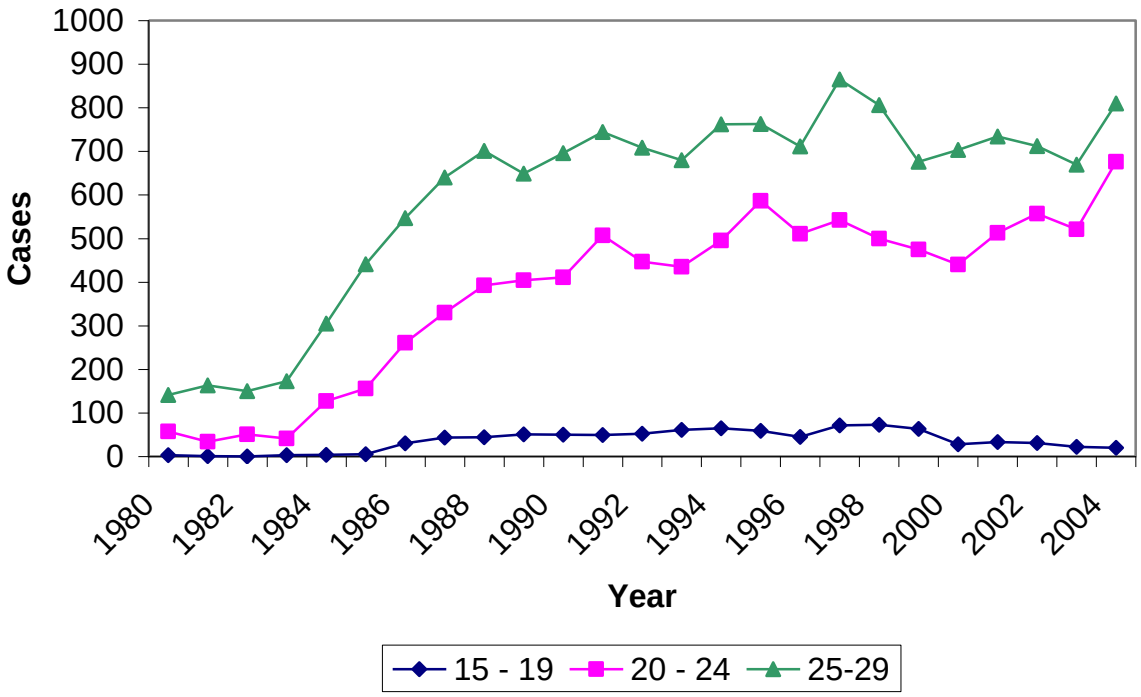
	Number of Diagnoses of CIN1-3 in 20 - 24 year olds, 2007		
NHS Board / Area / Reporting Laboratory	**CIN1**	**CIN2**	**CIN3**
Grampian / Orkney / Shetland 2007-2008	183	139	66
Tayside	21	51	67
Ayreshire & Arran	37	39	45
Lothian	89	108	98
Borders (Analysed at Lothian)	18	10	15
Fife	46	44	36
South Glasgow	42	45	21
North Glasgow	103	133	3
Forth Valley	60	103	42
Argyll & Clyde (Not sure what health board this goes Lanarkshire	13	26	26
Highland / Western Isles	20	34	34
Total	**632**	**732**	**453**

Figures from Lanarkshire are pending.

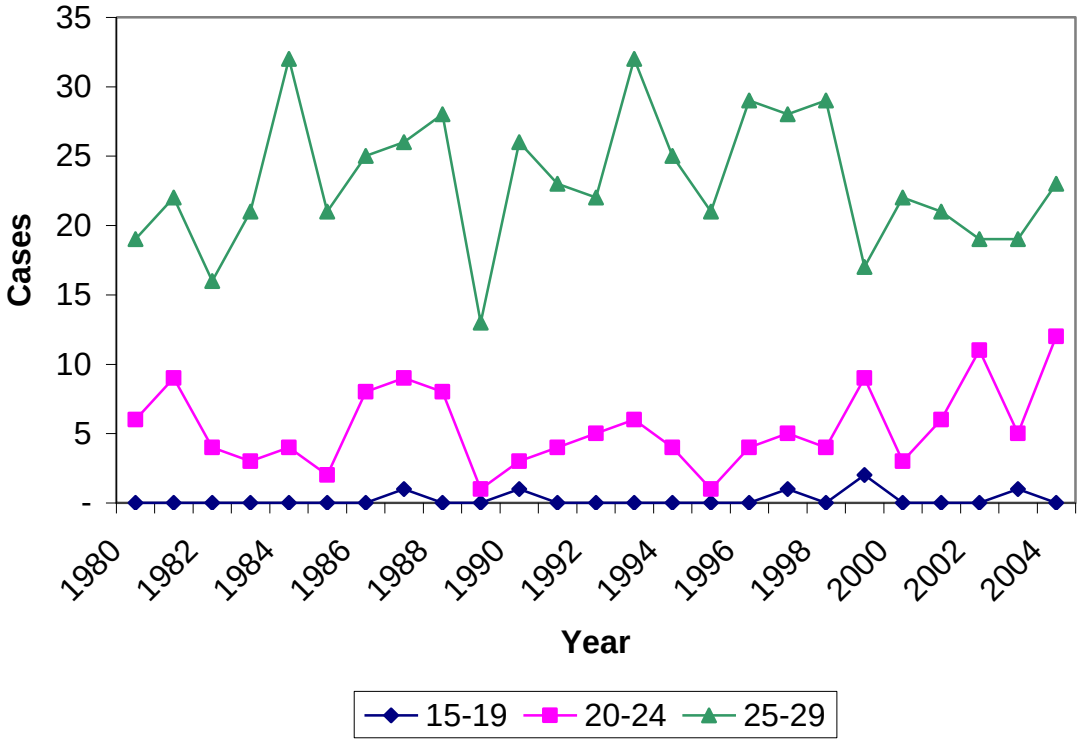
Lanarkshire accounts for 14% of all smears. Assuming it accounts for 14% of all abnormalities, the estimated total based on reported figures would be: 721 CIN1, 835 CIN2 and 516 CIN3**.** There were 676 new registrations of CIN3 in 2004 and 521 in 2003, so these figures don't seem too far off. These figures represent an under-ascertainment of CIN1s, as laboratories only record the results of pathology and the majority of CIN1s will not require a biopsy, thus the true figure, diagnosed from colposcopy is likely to be much higher.

The number of registrations of CIN3 (carcinoma in situ of the cervix uteri) is increasing in the age-group targeted for surveillance (20 to 24 year olds) (Figure 1), and there appears to be an upward trend in the number of registrations of cancer of the cervix uteri, although it is difficult to interpret this given the large variation in the curve.

Number of Registrations of Carcinoma in Situ (CIN3) of the Cervix Uteri, Scotland, 1980 - 2004

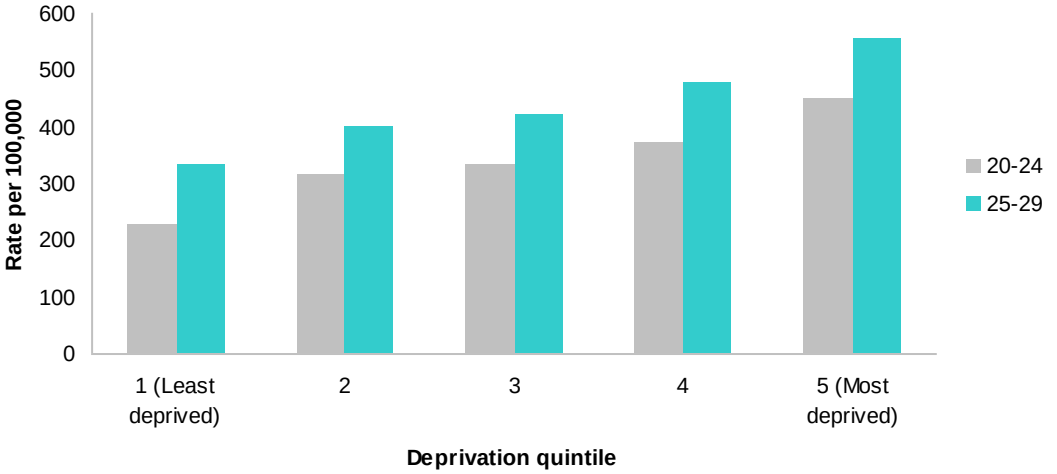


Number of Registrations of Cancer of the Cervix Uteri, Scotland, 1980 - 2004



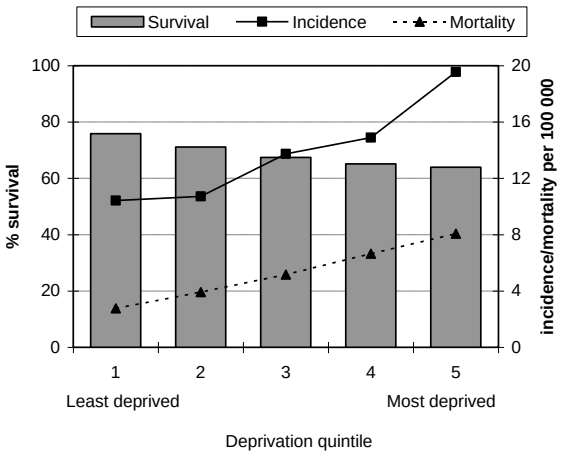
The incidence of carcinoma in situ of the cervix uteri is strongly correlated with social deprivation in 20 to 24 year olds (Figure 3). The age-specific incidence rate for this age-group was 226.4 cases per 100,000 person years at risk in those from areas of least deprivation compared to 447.5 cases per 100,000 person years at risk in those from areas of the highest social deprivation.

Carcinoma in situ of cervix uteri (ICD-10 D06)
Age-specific incidence rates by SIMD 2001 deprivation quintile



For all ages, the incidence and mortality due to cancer of the cervix uteri is correlated with social deprivation and survival is inversely correlated with deprivation (Figure 4).

Cancer of the cervix uteri (ICD-9 180)
Incidence[1], mortality[1] and cause-specific survival[2,3] at 5 years by deprivation quintile
Patients diagnosed 1991-95



Tests for trend across deprivation categories:

Incidence (p<0.01, linear regression on log rates);
Mortality (p<0.01, linear regression on log rates);
Survival (p<0.01, Cox regression).

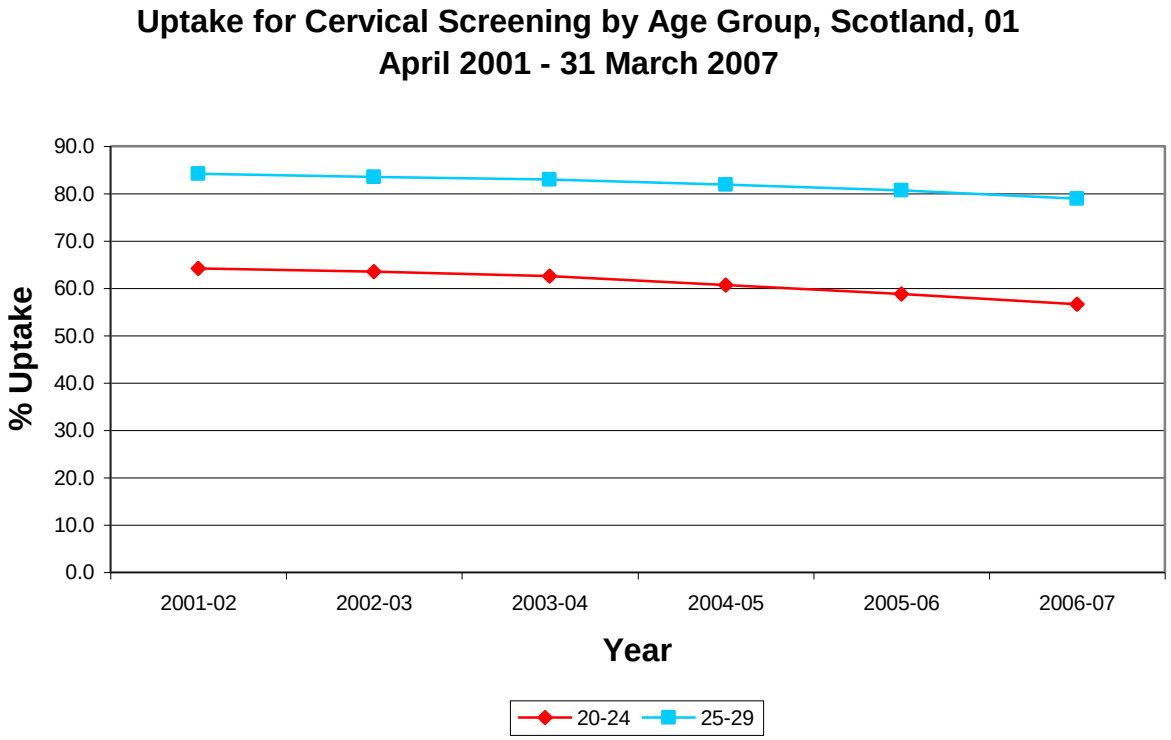
Deprivation quintile	Incidence (EASR)	Mortality (EASR)	Survival % at 5 years
1	10.4	2.8	75.9
2	10.7	3.9	71.1
3	13.7	5.2	67.5
4	14.9	6.7	65.1
5	19.6	8.1	63.9

[1]Age-standardised rates per 100 000 person-years at risk (European standard population).
[2]Adjusted for age.
[3]Cases diagnosed in 1994 and 1995 do not have 5 years' follow up.

Source: ISD publication '*Trends in Cancer Survival in Scotland 1971-1995*'

Uptake of cervical screening.

National data and data from Greater Glasgow and Clyde NHS Board indicate that uptake of cervical screening is inversely related to both age (Figure 5) and social deprivation. The uptake, for all of Scotland, in those aged 20 to 24 years of age is particularly low at less than 60%. In Greater Glasgow and Clyde NHS Board the 5.5 year screening uptake in 2005/2006 varied from 86% in areas of lowest deprivation to 74% in the areas of highest deprivation [3].



Incidence of Abnormal Smears by Age in Scotland

Currently the only data for this is for the 3rd and 4th quarters of 2007 in Lothian. Lothian accounted for 20% of all smears in all ages in 2007, so the Scottish total was estimated by multiplying the Lothian total by 5.

Table 3: Estimated total number of smears by grade of abnormality, Scotland, 2007

	Lothian Qtrs3/4, 2007	Lothian Estimated Total 2007	Scotland Estimated Total 2007*
Unsatisfactory	98	196	980
Negative	3487	6974	34870
Borderline Squamous	475	950	4750
Mild Dyskaryosis	300	600	3000
Borderline Glandular	5	10	50
Moderate Dyskaryosis	65	130	650
Severe Dyskaryosis	40	80	400
Severe Dyskaryosis / ?Invasion	1	2	10
Glandular Abnormality	0	0	0
Endocervical Adenocarcinoma	0	0	0
Other Malignancy	0	0	0
Total	4471	8942	44710

The prevalence of HPV by grade of cervical abnormality, outcomes of previous UK studies.

Study	Location	Year	Results	Authors
3444 randomly selected routine LBC specimens	Lothian	2000	HR-HPV – 92% (86/94) High-grade dyskaryosis - 87% (112/129) low grade dyskaryosis - 72% (82/114) borderline dyskaryosis HR-HPV - 12.7% < 25 years HPV-16 - 3.4% (105/3089) negative -28% (69/243) low-grade (borderline/ mild dyskaryosis) -49% (46/94) high-grade dyskaryosis HPV-18 - 1.4% (105/3089) negative -9.5% (69/243) low-grade (borderline/ mild dyskaryosis) -11.7% (46/94) high-grade dyskaryosis HPV-31 - 18% high-grade lesions. HPV-73 - 11% of high-grade & 6% of low-grade lesions.	Cuschieri et al. [2]
24510 women aged 20 to 64 years attending for routine cervical screening	Manchester Artistic Trial	2006	Women aged 20 to 24 years: - 40% HR-HPV 96% severe, 86% moderate & 70% mild dyskaryosis 31% of borderline smears and 10% of those with normal cytology positive for HPV HPV-16 and 18 in 64% of those with severe or worse cytology and in 2% of those with normal cytology. Other HPV types were found to account for 30% of high-grade disease. 20 to 29 years old, 22% of those with normal cytology, 55% of those with borderline cytology, 87% of those with mild dyskaryosis, 92% of those with moderate dyskaryosis and 99% of those with severe dyskaryosis were positive for HR-HPV	Kitchener et al [3]

Appendix 5: Glossary of Terms

Cervical Intraepithelial Neoplasia (CIN): Precursor lesion of squamous cell cervical cancer, histologically defined and graded: CIN1, CIN2 or CIN3 according to increasing severity:

CIN1: Low grade disease. Mild dysplasia or abnormal cell growth. The abnormalities are most apparent in the basal one third of the epithelium.

CIN2: High grade disease. Moderate dysplasia. The abnormalities are most apparent in the basal two thirds of the epithelium.

CIN3: High grade disease. Severe dysplasia spans greater than two thirds of the entire epithelium and may involve the full thickness. Sometimes referred to as cervical carcinoma in situ. The degree of nuclear atypia is greater than in either of the two lower grades

Dyskaryosis: Abnormal changes in cell nuclei. Used by the British Society for Clinical Cytology for classification of squamous cell abnormalities detected through cervical cytology. Three categories of dyskaryosis exist: mild dyskaryosis, moderate dyskaryosis and severe dyskaryosis according to increasing severity.

Dysplasia: Abnormality of development; in pathology, alteration in size shape and organisation of adult cells