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Contents

1 Introduction

Finland introduced the 10-valent pneumococcal conjugate vaccine (PCV10, Synflorix®, GSK) into the national infant vaccination programme in September 2010. This document describes the surveillance system and analysis methods for continuous monitoring of the population impact of the national vaccination programme (NVP), as implemented by the National Institute for Health and Welfare (THL). THL is a Finnish research and development institute operating under the Ministry of Social Affairs and Health, which was formed on 1 January 2009, with the merger of the National Public Health Institute of Finland (KTL) and the National Research and Development Centre for Welfare and Health (STAKES).

The background and rationale for the effectiveness evaluation are presented in Section 2. In Section 3, the existing data sources and surveillance methods for pneumococcal disease are described, including the IPD incidence. The fourth Section elaborates on the enhanced surveillance methods put in place after the introduction of NVP, including plans for analysis. Section 5 deals with reporting issues.

2 Background

2.1 Rationale

Pneumococcal conjugate vaccines (PCVs) have been shown to reduce burden of *Streptococcus pneumoniae* diseases, not only through direct protection provided to the vaccinated children but also through indirect protection of the unvaccinated children and adults. In the U.S., where infants have been vaccinated with the 7-valent PCV (PCV7, Prevenar®, Pfizer) since 2000 (and with PCV13 since 2010), the incidence of Invasive Pneumococcal Disease (IPD) has decreased considerably in all age groups. In addition, hospitalization rates for pneumonia have also markedly decreased after introduction of PCV7 into NVP in the U.S., for children younger than 2 years but also for adults aged 18-39 years. However, the decreases in IPD due to the vaccine serotypes has in some regions been accompanied by increases in IPD caused by non-vaccine serotypes, especially serotype 19A.

Continuous monitoring of pneumococcal diseases and evaluation of the population impact of PCVs are an essential part of all vaccination programs after implementation. As Finland has recently introduced PCV for children, THL will monitor closely the epidemiology of IPD, but also occurrence of pneumonia and acute otitis media (AOM) through national health registers to assess the overall public health benefits of the program.

Finland is especially suitable for surveillance due to long tradition of established health registers for the whole country, universal use of unique and life-long Personal Identity Code for each Finnish citizen, expected high coverage of NVP, and public health care system equally accessible for each citizen.

2.2 Pneumococcal vaccination in Finland

According to vaccine sales data obtained from the Finnish pharmacy records, the private sector use of PCVs (PCV7 licensed in February 2001, PCV10 (Synflorix by GSK) in March 2009, and PCV13 (Prevenar 13 by Pfizer) in December 2009), has been minimal since their licensure (an average of 100 doses/month). The use of 23-valent polysaccharide vaccine in the adult and elderly population has been similarly infrequent.

Finland introduced PCV10 (Synflorix, GSK) in NVP for a period of two years in September 2010 after public tender, which is currently repeated every two years. The target group is all children born at or after June 1, 2010. The vaccination schedule is 2 primary doses at the ages of 3 and 5 months and a booster dose at 12 months of age. The vaccines are administered concomitantly with other NVP vaccinations in Finland. No catch-up vaccination schedules are used. For children with risk factors for pneumococcal disease PCV administration for older children up to 4 years of age is also recommended followed by one polysaccharide dose after 2 years of age.

In May 2009, before PCV was introduced to the NVP, THL started the Finnish Invasive Pneumococcal disease vaccine effectiveness (FinIP) trial, in co-operation with 80% of Finnish health care centers and GSK, to evaluate the overall effectiveness of PCV10 in the population. The FinIP trial was designed as a community-randomized, double-blind trial and will enable the evaluation of the overall effectiveness of the PCV10 against IPD by measuring the effects both among vaccinated children (direct and indirect effects, i.e. total effects) and among unvaccinated children and adults (indirect effects i.e. herd effects). Two thirds of the study clusters use PCV10 and one third of the clusters are control areas, in which the children receive either the hepatitis B vaccine (children aged 6 weeks to 11 months at enrolment) or hepatitis A vaccine (children aged 12 to 18 months at enrolment). Effectiveness of immunization according to a 2-dose or 3-dose primary schedule, followed by a booster dose, will also be assessed in the randomized study setting among children enrolled <7 months of age. In addition to IPD, the trial will evaluate total and indirect vaccine impact on the incidence of hospital-diagnosed pneumonia, as well as the vaccine's impact on tympanostomy tube placement and outpatient prescriptions of antimicrobial agents. All outcome data for the FinIP trial will be collected from the national registers.

Since approximately 50,000 children are participating and vaccinated in the FinIP trial, this needs to be taken into account, and utilized when possible, in the evaluation of the overall NVP impact; see Section 4 for further details.

3 Existing surveillance systems and data sources

3.1 Register data sources for pneumococcal disease

The following national registers will be used in the evaluation of PCV NVP:

- National Infectious Disease Register, maintained by KTL/THL since 1995
  - o Invasive pneumococcal disease (incl. serotyping and antimicrobial susceptibility)
- National Care Register maintained by STAKES/THL since 1994
  - o Hospital-diagnosed pneumonia (ICD-10 coded)
  - o Tympanostomy tube placement (performed in public health care)
- Social Insurance Institution register
  - o Tympanostomy tube placement (performed in private health care) (since 1964)
  - o Outpatient prescriptions of antimicrobial agents (since 1995, since 2006 in the current form)

The primary data source for the NVP PCV evaluation is the National Infectious Disease register (NIDR) which is a population-based and laboratory-based surveillance system. It includes all IPD isolates reported by the Finnish clinical microbiology laboratories. A case of IPD, defined by detection by culture either from blood or cerebrospinal fluid, is typically recorded into the NIDR within 2 weeks of the date of sample collection. Duplicate reports of cases within 3 months are merged into episodes at THL. The reference laboratories at THL provide serotyping and antimicrobial susceptibility data for the pneumococcal isolates. Until 2009, serotyping was performed at THL laboratory in Oulu, where latex agglutination and counterimmunoelectrophoresis and quellung reaction (when needed) were used. Since 2010, serotyping has been performed at THL laboratory in Helsinki, where PCR-based serotyping and quellung reaction (when needed) are used. Determination of antimicrobial susceptibility for penicillin, erythromycin, tetracycline, levofloxacin, clindamycin and ceftriaxone is performed at THL laboratory in Turku for all IPD isolates using the agar dilution method, usually within 2 to 6 months of the receipt of the isolate. Additionally, the FiRe project (FiRe - Finnish Study Group for Antimicrobial Resistance), coordinated by THL annually collects clinically performed, aggregated antimicrobial susceptibility data. Further information is available at http://www.finres.fi/index.php?id=12. The FiRe data also include other than IPD isolates, e.g. middle ear discharge specimens from children with AOM. The availability and usefulness of these data in the evaluation of the PCV programme will be explored.

Other clinical syndromes potentially caused by pneumococcus are, among others, pneumonia and AOM. The National Care Register (HILMO) contains all outpatient and inpatient diagnoses (ICD10) given at Finnish hospitals. The HILMO has been operational since 1994, and has included outpatient visits since 1999. In accordance with the current legislation, the data accumulates to the HILMO in yearly batches. The data is available approximately 9 months after the new year.

Social Insurance Institution maintains a register that has been operational since 1964 with multiple changes and adaptations to current Finnish laws. Expanding data has been collected on national insurance reimbursements including drug prescriptions since 1995. From 2006 onwards all prescription medications bought from pharmacies are included in this register. Between 1995 and 2006 only purchases of drugs that were covered by the national insurance reimbursement were included in the register. Thus, e.g. cheap antibiotics with lower expense than the reimbursement level were not included in the register before 2006. Delay for data collection purposes is minimum 6 weeks.

3.2 Invasive pneumococcal disease

Compared to other European countries, the incidence of IPD in Finland is relatively high, yet considerably lower than in the U.S. before the PCV introduction. Table 1 shows the recent IPD frequencies by age group and calendar year in Finland. The average incidence in age groups 0 to 1, 2 to 64, and over 65-year-olds during 2004-2010 were, respectively, 60, 11, and 32 cases per 100,000 person-years.

Table 1: IPD frequencies by age and calendar year

Calendar year	0-1 years	2-64 years	65 and over	Total
2004	70	440	239	749
2005	73	435	230	738
2006	82	394	271	747
2007	78	418	295	791
2008	65	533	328	926
2009	62	498	295	855
2010	61	471	304	836

3.3 NVP vaccination coverage in Finland

Based on bi-annual coverage surveys conducted by the Department of Vaccination and Immune Protection, the uptake of PCV is expected to be over 95% in the NVP. Infant and childhood vaccines are administered in the municipal well-baby clinics, which are attended 8 times by 12 months of age by practically all children born in Finland. The total population of Finland is 5.3 million with mainly Caucasian origin. The annual birth cohort is approximately 60 000.

In addition to bi-annual coverage surveys, THL is in the process of implementing an online nationwide vaccination register. This register is expected to become operational during 2012. Vaccination register will be utilized in the follow-up of PCV vaccine coverage.

4 Enhanced surveillance and analysis plan

4.1 Follow-up of breakthrough cases of invasive pneumococcal disease

Enhanced surveillance of all IPD reports for children born after 1 June, 2010, i.e. eligible for the national PCV vaccination programme, has been set up. A notification of any IPD case occurring in this age-group is sent online from the NIDR to the Department of Vaccination and Immune protection. Subsequently, vaccination information is verified from the medical records at primary health care. The serotyping of IPD isolates from children is prioritized at THL reference laboratory.

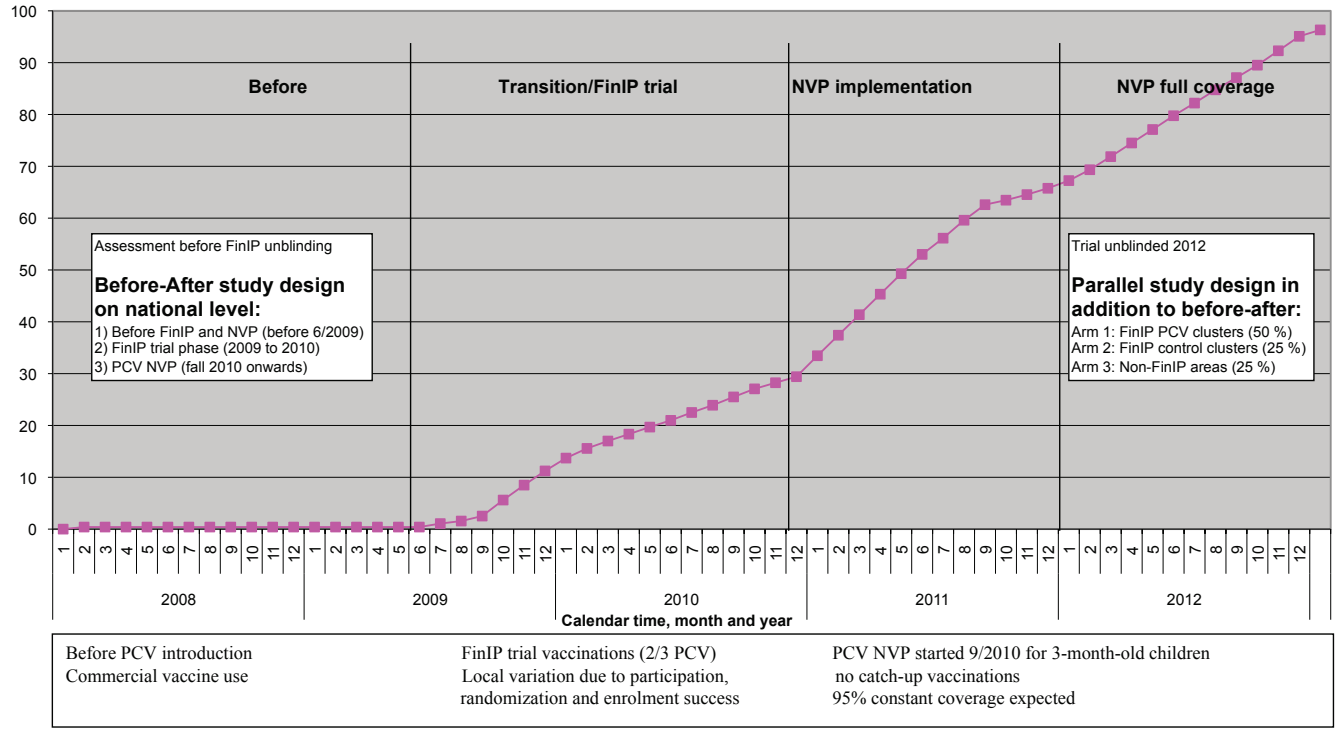
4.2 Populations under surveillance

The total (i.e. the sum of direct and indirect) effectiveness of the NVP will be evaluated among children born after 1st of June 2010. Indirect effectiveness will be evaluated in those born before 1st of June 2007, stratified by age. Those born between June 2007 and June 2010 have largely been eligible for the FinIP study, and will mainly be evaluated in the trial setting.

Further risk group stratifications, such as based on low birth weight, will be subsequently performed. However, due to relatively small birth cohort in Finland, it is expected that sufficient power for the evaluation of total effectiveness in any subgroup analysis is achieved only after several years of surveillance (see also Table 1).

Figure 1 depicts the assumed increase in vaccination coverage for children under 2-years of age.

Figure 1. PCV NVP effectiveness surveillance designs in Finland based on estimated national coverage of PCV vaccinations in children under 2 years of age



4.3 Pneumococcal disease outcomes to be monitored

The following outcomes will be used for the population effectiveness:

- Invasive pneumococcal disease
- Hospital-diagnosed pneumonia
- Tympanostomy tube surgery
- Outpatient treatment with antimicrobial agents

Because of the low specificity of other outcomes than IPD, and delays of data accumulation in other registers than NIDR, the primary focus will be on IPD. The rates of IPD will be further stratified according to the serotypes and –groups covered by the PCV in the NVP (currently: PCV10 types, PCV10-related, and non-PCV10 types) and antimicrobial resistance. Other outcome evaluations are conditional on acceptance of relevant research permissions.

4.4 Comparison of the rates of pneumococcal diseases

The rates of disease endpoints will be compared both between and within calendar time (i.e before/after and in parallel time, see also Figure 2). Calendar time evaluation will be performed in three phases:

1) Before the start of the FinIP trial
2) FinIP trial phase
3) After implementation of PCV NVP

After the unblinding of the FinIP trial in 2012, three distinct areas in Finland can also be identified for parallel comparison:

1) Area in the FinIP trial where PCV10 was administered (50% of the population)
2) Area in the FinIP trial where control vaccine was administered (25% of the population)
3) Area not included in the FinIP trial (25% of the population)

4.5 Additional studies

An annual report on the population effectiveness of the National PCV vaccination programme will be published in Finnish and English on the public website of THL by May/June each year, beginning from 2012. Because of the register data delays, this report will include data extracted from NIDR and KELA registers up to the year prior to the reporting year, and data extracted from HILMO up to two years prior to the reporting year. The primary focus will be on the investigation of changes in the incidence of IPD, with a special emphasis on the total and indirect effectiveness, including serotype distribution and antimicrobial resistance.

5 Reporting

An annual report on the population effectiveness of the National PCV vaccination programme will be published in Finnish and English on the public website of THL by May/June each year, beginning from 2012. This report will include data extracted from NIDR and KELA registers up to the year prior to the reporting year, and data extracted from HILMO up to two years prior to the reporting year. The primary focus will be on the investigation of changes in the incidence of IPD, with a special emphasis on the total and indirect effectiveness.

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