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**Accelerated Development of VAccine beNefit-risk  
Collaboration in Europe**


Grant Agreement n°115557

**D4.1 Report on appraisal of methods  
for vaccine coverage, burden of  
disease and vaccine benefits**

**WP4 – Methods for burden of disease, vaccination coverage, vaccine  
safety & effectiveness, impact and benefit risk monitoring**


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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## TABLE OF CONTENTS


<b>DOCUMENT INFORMATION</b> .....	<b>5</b>
<b>DOCUMENT HISTORY</b> .....	<b>6</b>
<b>DEFINITIONS AND ABBREVIATIONS</b> .....	<b>7</b>
<b>EXECUTIVE SUMMARY</b> .....	<b>9</b>
<b>PART I: VACCINE COVERAGE</b> .....	<b>10</b>
<b>1. INTRODUCTION</b> .....	<b>11</b>
<b>2 REVIEW OF PUBLISHED DATA ON VACCINE COVERAGE METHODS</b> .....	<b>12</b>
2.1 REVIEW METHODS .....	12
2.2 RESULTS .....	12
2.2.1 <i>Diphtheria</i> .....	12
2.2.2 <i>Pertussis</i> .....	14
2.2.3 <i>Tetanus</i> .....	15
2.2.4 <i>Pneumococcus</i> .....	15
2.2.5 <i>Human papillomavirus (HPV)</i> .....	17
2.2.6 <i>Influenza</i> .....	18
<b>3 DESCRIPTION AND DEFINITION OF VACCINE COVERAGE METHODS</b> .....	<b>20</b>
3.1 ADMINISTRATIVE METHOD .....	20
3.2 SURVEY METHODS .....	21
3.3 INDIVIDUALLY LINKED DATA FROM REGISTRIES.....	21
<b>4 DESCRIPTION OF VARIOUS DATA TYPES</b> .....	<b>22</b>
4.1 NUMERATOR DATA .....	23
4.1.1 <i>Aggregated number of vaccines sold</i> .....	23
4.1.2 <i>Aggregated number of vaccines distributed</i> .....	23
4.1.3 <i>Aggregated number of vaccines administered</i> .....	23
4.1.4 <i>Number of subjects vaccinated</i> .....	23
4.1.5 <i>School or day care records</i> .....	24
4.1.6 <i>Reimbursement data</i> .....	24
4.2 DENOMINATOR DATA .....	25
4.3 OTHER TYPES OF DATA.....	26
<b>5 OVERVIEW OF COVERAGE ESTIMATION METHODS</b> .....	<b>27</b>
5.1 TABLES SHOWING COVERAGE ESTIMATION METHODS.....	27
<b>6. ELECTRONIC REGISTRATION OF VACCINES</b> .....	<b>33</b>
6.1 SALES OF VACCINES: WHOLESALERS TO PHARMACIES, SALES TO VACCINATION CLINICS AND GPs .....	33
6.2 PRESCRIPTION DATABASES, HEALTH RECORDS FROM GPs, HOSPITALS OR WELL-VISIT CLINICS .....	33
6.3 VACCINATION REGISTRIES .....	34
6.3.1 <i>Denmark</i> .....	34
6.3.2 <i>Norway</i> .....	35
6.3.3 <i>Sweden</i> .....	35
6.3.4 <i>SVEVAC</i> .....	37
6.3.5 <i>Iceland</i> .....	37
6.3.6 <i>Finland</i> .....	37
6.3.7 <i>The Netherlands</i> .....	38
6.3.8 <i>Belgium</i> .....	38
6.3.9 <i>England</i> .....	39

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

6.3.10 Ireland .....	40
6.3.11 Spain .....	41
6.3.12 Portugal .....	42
6.3.13 Italy .....	43
6.3.14 Slovenia .....	45
6.3.15 Malta .....	45
6.3.16 Other European countries .....	47
<b>7. DISCUSSION OF RESULTS .....</b>	<b>48</b>
7.1 IN GENERAL .....	48
7.2 HOW COMPARABLE ARE VACCINE COVERAGE ESTIMATES BETWEEN COUNTRIES .....	48
<b>8 CONCLUSIONS AND RECOMMENDATIONS .....</b>	<b>50</b>
<b>9 REFERENCES .....</b>	<b>52</b>
<b>PART II: BENEFITS OF VACCINES AND VACCINATION PROGRAMMES .....</b>	<b>78</b>
<b>ABBREVIATIONS .....</b>	<b>79</b>
<b>1. INTRODUCTION .....</b>	<b>80</b>
<b>2. PERSPECTIVES ON BENEFIT ASSESSMENT .....</b>	<b>80</b>
2.1 THE PERSPECTIVE OF PUBLIC HEALTH AUTHORITIES. ....	80
2.2 THE PERSPECTIVE OF REGULATORS. ....	80
2.3 THE VACCINE MANUFACTURERS' PERSPECTIVE. ....	80
<b>3. DEFINITIONS OF MEASURES FOR BENEFITS OF VACCINATION AND VACCINATION PROGRAMMES .....</b>	<b>81</b>
<b>4. CRITERIA TO ASSESS METHODS .....</b>	<b>82</b>
4.1 STATISTICAL CRITERIA. ....	82
4.2 TEMPORAL CRITERIA. ....	82
4.3 ROBUSTNESS CRITERIA. ....	83
4.4 OPERATIONAL CRITERIA. ....	83
4.5 ETHICAL CRITERIA .....	83
<b>5. METHODS OF VACCINE BENEFITS ASSESSMENT PRE-IMPLEMENTATION OF NATIONAL VACCINE RECOMMENDATIONS .....</b>	<b>83</b>
5.1 RANDOMISED CONTROLLED TRIALS .....	83
5.1.1 Individually randomised controlled trial (RCT).....	83
5.1.2 Cluster randomised trials.....	84
5.2 STEPPED WEDGE DESIGNS FOR VACCINE INTRODUCTION .....	84
5.3 BURDEN OF DISEASE (BOD) ASSESSMENTS PRE-IMPLEMENTATION OF VACCINATION PROGRAMMES....	84
5.3.1 Vaccine probe studies .....	85
<b>6. METHODS FOR VACCINE BENEFIT ASSESSMENT POST-IMPLEMENTATION OF NATIONAL VACCINE RECOMMENDATIONS .....</b>	<b>85</b>
6.1 VACCINE EFFECTIVENESS: EPIDEMIOLOGICAL METHODS .....	85
6.1.1 Cohort studies .....	86
6.1.2 Case referent studies .....	86
6.1.3 Household studies.....	88
6.1.4 Effectiveness against post-infection outcomes (severity and infectiousness).....	89
6.2 VACCINE EFFECTIVENESS: MATHEMATICAL MODELS .....	89
6.2.1 Modelling to estimate separate components of vaccine effectiveness.....	89
6.2.2 Models to study changes in vaccine effectiveness over time.....	91
6.3 INDIRECT VACCINE EFFECTS.....	91
6.4 VACCINE FAILURE.....	92

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

6.5	INTERPRETATION OF VACCINE EFFICACY AND EFFECTIVENESS ESTIMATES .....	92
6.5.1	<i>Causality: efficacy and effectiveness</i> .....	92
6.5.2	<i>Mode of protection: All-or-nothing versus leaky</i> .....	92
6.5.3	<i>Effectiveness against infection, carriage, illness, severe illness, death, infectivity</i> .....	93
6.5.4	<i>Direct and indirect effects</i> .....	93
6.6	IMPACT OF VACCINATION: EPIDEMIOLOGICAL METHODS .....	93
6.6.1	<i>Impact on disease occurrence</i> .....	93
6.6.2	<i>Impact on the burden of disease</i> .....	94
6.7	IMPACT OF VACCINATION: MATHEMATICAL MODELS .....	95
6.7.1	<i>Modelling dynamic effects when there is no endemic equilibrium</i> .....	95
6.7.2	<i>Extrapolating from intermediate outcomes to disease endpoints</i> .....	96
6.7.3	<i>Modelling herd-protection</i> .....	96
6.7.4	<i>Modelling long-term dynamic effects (beyond the 'honeymoon-period')</i> .....	97
6.8	IMMUNOGENICITY AND CORRELATES FOR PROTECTION .....	97
6.9	SERO-EPIDEMIOLOGY .....	98
<b>7.</b>	<b>EVALUATION OF THE AVAILABLE METHODS</b> .....	<b>98</b>
7.1	EFFECTIVENESS METHODS .....	98
7.1.1	<i>Pre-implementation of a national vaccine recommendation</i> .....	99
7.1.2	<i>Post-implementation of a national vaccine recommendation</i> .....	99
7.2	IMPACT METHODS .....	101
7.3	BURDEN OF DISEASE METHODS .....	101
7.4	IMMUNOGENICITY AND SERO-EPIDEMIOLOGY .....	102
<b>8.</b>	<b>EXPERIENCE FROM OTHER PROJECTS AND SYSTEMS</b> .....	<b>102</b>
8.1	EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMOLOGY AND PHARMACOVIGILANCE .....	102
8.2	I-MOVE .....	103
<b>9.</b>	<b>CONCLUSIONS AND RECOMMENDATIONS</b> .....	<b>103</b>
<b>10.</b>	<b>REFERENCES</b> .....	<b>104</b>
<b>ANNEXES</b>	.....	<b>111</b>
<b>ANNEX I VACCINE COVERAGE</b>	.....	<b>112</b>
<b>ANNEX II BENEFITS 1: QALY AND DALY COMPUTATION</b>	.....	<b>132</b>
<b>ANNEX III ADVANCE DOSSIER FOR REVIEW OF METHODS TO ASSESS BENEFITS</b>	.....	<b>134</b>

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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### PART I : VACCINE COVERAGE

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<b>Description of the</b>	This deliverable aims to appraise the currently used and available methods
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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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## DEFINITIONS AND ABBREVIATIONS

### ABBREVIATIONS


- Participants of the ADVANCE Consortium are referred to herein according to the following codes:
  - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
  - **UNIBAS.** Universitaet Basel (Switzerland) - **Managing entity of the IMI JU funding**
  - **EMA.** European Medicines Agency (United Kingdom)
  - **ECDC.** European Centre for Disease Prevention and Control (Sweden)
  - **SURREY.** The University of Surrey (United Kingdom)
  - **P95.** P95 (Belgium)
  - **SYNAPSE.** Synapse Research Management Partners, S.L. (Spain)
  - **OU.** The Open University (United Kingdom)
  - **LSHTM.** London School of Hygiene and Tropical Medicine (United Kingdom)
  - **PEDIANET.** Società Servizi Telematici SRL (Italy)
  - **KI.** Karolinska Institutet (Sweden)
  - **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
  - **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
  - **AUH.** Aarhus Universitetshospital (Denmark)
  - **UTA.** Tampereen Yliopisto (Finland)
  - **WIV-ISP.** Institut Scientifique de Santé Publique (Belgium)
  - **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
  - **SSI.** Statens Serum Institut (Denmark)
  - **RCGP.** Royal College of General Practitioners (United Kingdom)
  - **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu \* National Institute for Public Health and the Environment (Netherlands)
  - **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
  - **SP.** Sanofi Pasteur (France)
  - **NOVARTIS.** Novartis Pharma AG (Switzerland)
  - **SP MSD.** Sanofi Pasteur MSD (France)
  - **CRX.** Crucell Holland BV (Netherlands)
  - **PFIZER.** Pfizer Limited (United Kingdom)
  - **TAKEDA.** Takeda Pharmaceuticals International GmbH (Switzerland)
- **DTP.** Diphtheria-Tetanus-Pertussis
- **GP.** General practitioners
- **HPV.** Human papillomavirus

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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- **UK.** United Kingdom
- **VENICE.** Vaccine European New Integrated Collaboration Effort
- **WHO.** World Health Organisation

## DEFINITIONS

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ADVANCE project (115557).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ADVANCE Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst ADVANCE participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
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## EXECUTIVE SUMMARY

This deliverable aims to appraise the currently used and available methods for vaccine coverage, burden of disease and effectiveness assessment of vaccines and vaccination programs.

The first part of this report presents currently used vaccination coverage estimation methods in Europe. Based on a search in the published literature and reports from the Vaccine European New Integrated Collaboration Effort (VENICE) consortium, it is evident that there is currently no standardized method to estimate or report vaccine coverage in Europe. Three estimation methods are used; the administrative method, the survey method and computerised records.


The most commonly used denominators in the administrative and the computerised methods are, at 12 months, at 24 months, at school entry and birth cohorts. The choice of denominator is important for the comparability of data. The fixed months (12 and 24 months) will not allow vaccines received after these months to be included in the coverage estimates. In contrast, countries using birth cohorts can continuously update their coverage estimates for each birth cohort. This implies that the coverage estimates obtained using fixed months most likely will underestimate coverage compared with estimates obtained using birth cohorts thus these two types of estimates might not be readily comparable. Several EU countries already have or are developing computerised vaccination registers. These registers allow continuous vaccine coverage estimation that is not bound to a specific age in months. When both timeliness and vaccine exposure should be taken into account we recommend to use these registers to identify the optimal time for vaccination coverage estimation for each vaccine dose across countries.

In the second part of the report an overview is provided of methods for assessing benefits of vaccines and vaccination programmes. Here benefits are divided in two main areas: vaccine effectiveness and impact. Methods are divided in epidemiological methods and methods based on mathematical modelling. After the inventory of existing methods, an assessment of gaps, strengths and weaknesses is carried out, by taking into account the perspectives of public health, regulatory authorities, vaccine manufacturers and academia. Our assessment of methods is carried out focussing on their performance to deliver evidence for policy decisions about the use of vaccines. Based on this assessment, conclusions are formulated which should form the basis for guiding proof of concept studies and work on the extension of methods.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
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## PART I: VACCINE COVERAGE

Hanne-Dorthe Emborg, Anna Cantarutti, Lieke van der Aa,  
& Victoria Abbing-Karahagopian

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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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## 1. INTRODUCTION

Vaccines represent one of the most effective and cost-saving public health interventions (<http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>). Some vaccines provide almost lifelong protection against a specific infection, while other vaccines must be repeated with certain time intervals. In order to evaluate the benefit and risks of each vaccine and the public health impact of the vaccination programmes, it is important to estimate the proportion of individuals within the target population who has received the vaccine (vaccine coverage).

Countries monitor vaccine coverage because it is:

- 1) one of the basic indicators used to monitor the performance of the health care system within a country and the data are provided to WHO yearly
- 2) important for assessing burden of illness of vaccine preventable diseases and monitor progress or set back in achievements to control a disease, e.g. eradication or elimination
- 3) required when assessing vaccine effectiveness by the screening method
- 4) important to determine the proportion of exposed when assessing safety signals, in particular when the systems are based on passive reporting of suspected adverse events

The aim of this report is to review existing data and methods that are currently being used in the EU to estimate vaccine coverage. To illustrate the different coverage estimation methods used in various countries we selected vaccines that are used in different target groups:


- 1) vaccines recommended for the childhood vaccination programme.
- 2) vaccines that are offered to young adults and elderly
- 3) vaccines recommended to risk groups

Accordingly, the following vaccines were selected for this report:

- 1) Diphtheria-Tetanus-Pertussis (DTP) vaccine
- 2) Pneumococcal vaccine
- 3) Human papillomavirus (HPV) vaccine
- 4) Influenza vaccine

The Diphtheria-Tetanus-Pertussis (DTP) vaccine is primarily a childhood vaccine. Vaccination schedules and vaccines used vary between countries because of different strategies to prevent pertussis. Some countries recommend booster in older age groups, whereas others do not. In addition, in the UK and Belgium, vaccination is recommended to pregnant women in order to protect infants from pertussis.

The Pneumococcal vaccine is in many countries recommended to both children and elderly people. Use of a conjugated pneumococcal vaccine in children creates herd immunity in elderly people.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
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The Human papillomavirus (HPV) vaccine is included in the national vaccination programme of many countries but the vaccination schedules and types of vaccines used vary between countries. The vaccine is given to adolescents, an age group that is not commonly vaccinated.

The Influenza vaccine is a vaccine that is administered every season, it may be recommended to elderly people, risk groups, pregnant women and children. However, the recommendation varies between European countries.

## 2 Review of published data on vaccine coverage methods

### 2.1 Review Methods

A broad literature search was performed using MEDLINE for each of the selected vaccines: influenza, human papillomavirus, pneumococcal, diphtheria, tetanus and pertussis. Only literature describing vaccination coverage estimation during the time period 2004 to 2014 in EU countries plus Norway and Switzerland were included. All identified literature was screened for relevance based on the title, keywords and the available abstract.

### 2.2 Results

#### 2.2.1 Diphtheria

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 3 2014>


Search Strategy:

```

-----
1  coverage.af. (53758)
2  uptake$.af. (157891)
3  1 or 2 (210761)
4  (vaccin$ or immuni$.sh. (130192)
5  diphtheria$.af. (6427)
6  diphteria$.af. (73)
7  dtp$.af. (12778)
8  5 or 6 or 7 (18578)
9  3 and 4 and 8 (637)
10 limit 9 to yr="2004-2014" (434)
*****

```

We identified a total of 434 abstracts regarding diphtheria vaccination coverage. Most abstracts originated from the USA or other parts of the world. Only 47 abstracts from the EU were eligible for inclusion. The number of abstracts and data type are listed by country in Table A1 in the Appendix.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
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From **France** 15 abstracts were identified. The abstracts described different diphtheria vaccine coverage surveys. Three surveys were national, one internet survey using a self-administered questionnaire on children aged 0-6 years (1), one school survey on children aged 6-years using two-stage sampling (school and pupils) (2) and one national survey among health care personnel (3). In the remaining studies, a subset of the population was included: children from a particular area, healthcare workers/students from selected hospitals or schools, risk groups and the adult population in different regions (4–15).

From **Germany** we identified 6 abstracts. One abstract described a national survey in the German population using vaccination cards and self-reports (16), a second abstract described national data from school health examinations including children and adolescents (17) and a third study described nationwide telephone interviews of children born from 1996-2003 (18). The remaining three abstracts described regional immunisation studies targeting the adult workforce, adolescents and children (19–22).

From **Switzerland**, five abstracts were identified. One study described the Swiss National Vaccination Coverage survey in children and adolescents (2, 8 and 16 years) this was a cross-sectional survey using two-stage sampling. Families were contacted by email and telephone and coverage was estimated by vaccination cards and vaccination summary forms (23). The remaining four abstracts described surveys among children from Geneva and Basel using e.g. vaccination cards (24–27).


Five abstracts from **Greece** were identified, describing surveys from healthcare workers, nursing students and adolescents (28–32).

From **Italy**, there were three abstracts; one was performed in children with chronic diseases (33) whereas the other two were performed in children from two different regions using questionnaire, vaccination cards and a regional registration system (34,35).

In two studies from Flanders, **Belgium** children were identified by cluster sampling; interviews were carried out and information was collected using vaccination documents (36,37). In addition, Lieke Van der Aa has identified two studies from Flanders and two from the French community. In the first study from Flanders parents of 915 infants aged 18-24 months and 1319 adolescents aged 13-14 years were interviewed at home (38) and in the second study in total 946 children and 1500 adolescents were included (39). The two studies from the French community were also surveys (40,41)

In two **Dutch** studies, a vaccination register was used to determine vaccination coverage per vaccination (dose) and the denominator was birth cohorts (42,43). In the third Dutch register study all children age 5 and 12 living in Amsterdam were included (44).

In the **UK**, quarterly or annually reports were used to compare systems for the teenager booster (given at school versus giving by GPs) (45).

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	14/140

One abstract from **Denmark** was using the childhood vaccination database to calculate national vaccination coverage (46).

Two abstracts from **Spain** were retained, one study compared vaccination coverage estimation based on questionnaires, serology and vaccines distributed (47), the other study looked at vaccination coverage in children in Catalonia using telephone interviews with parents (48).

From **Slovenia** there was a study in Roma children from three regions using health records, immunization records (booklets) and the National Computerized immunization system (CEPI 2000) (49). In addition, Serbia performed a study among Roma children (50).

Table A1 in the Appendix gives an overview of the diphtheria articles retained from the literature search.

This overview shows that most countries publish survey data, only the Netherlands, Denmark, Serbia and Slovenia have published coverage data using regional or national registries.


### 2.2.2 Pertussis

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 3 2014>  
Search Strategy:

- 
- 1 coverage.af. (53758)
  - 2 uptake\$.af. (157891)
  - 3 1 or 2 (210761)
  - 4 (vaccin\$ or immuni\$).sh. (130192)
  - 5 pertussi\$.af. (12884)
  - 6 3 and 4 and 5 (654)
  - 7 limit 6 to yr="2004-2014" (458)
- \*\*\*\*\*

In total, 458 abstracts were identified; the abstracts were from several different countries with the USA as the country with most abstracts. Only abstracts from EU countries were included. Some abstracts described only the epidemiology of pertussis, and hence were excluded. Articles describing a possible link between pertussis vaccine and a signal and articles describing immunogenicity using different vaccines or describing outbreaks were all excluded.

Eligible abstracts included 12 abstracts from **France** (1–7,9,10,12,14,51), six from **Germany** (16,52,17,53,20,18), five from **Switzerland** (23–27), three from **Greece** (30–32) and **Italy** (33–35) each, two each from **Belgium** (36,37) and **The Netherlands** (42,43) and one each from **Spain** (47), **Denmark** (46), **Slovakia** (49) and **Serbia** (50). The same four studies identified by Lieke Van der Aa under diphtheria also covers pertussis. A very large proportion

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

of the pertussis abstracts were the same as those identified in the diphtheria search. Table A2 in the Appendix gives an overview of the pertussis articles retained from the literature search.

### 2.2.3 Tetanus

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 3 2014>

Search Strategy:

```
-----
1 coverage.af. (53758)
2 uptake$.af. (157891)
3 1 or 2 (210761)
4 (vaccin$ or immuni$.sh. (130192)
5 dtp$.af. (12778)
6 tetanus$.af. (9195)
7 5 or 6 (21290)
8 3 and 4 and 7 (712)
9 limit 8 to yr="2004-2014" (474)
*****
```


In total 474 abstracts were identified, a large proportion of these studies were performed outside Europe, with USA as the country with most abstracts. This leaves 16 abstracts from **France** (1–15,54), eight from **Germany** (16–22,55), five from **Switzerland** (23–27), six from **Greece** (28–32,56), four from **Italy** (33–35,57), three from **Spain** (47,48,58), two from **Belgium** (36,37), three from the **Netherlands** (42–44) and one each from the **UK** (45), **Denmark** (46), **Slovakia** (49) and **Serbia** (50). The same four studies identified by Lieke Van der Aa under diphtheria also covers tetanus. A very large proportion of the tetanus abstracts were the same as identified in the diphtheria and pertussis search. Table A3 in the Appendix gives an overview of the tetanus articles retained from the literature search.

### 2.2.4 Pneumococcus

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 3 2014>

Search Strategy:

```
-----
1 coverage.af. (53758)
2 uptake$.af. (157891)
3 1 or 2 (210761)
4 (vaccin$ or immuni$.sh. (130192)
5 pneumo$.af. (141020)
6 3 and 4 and 5 (610)
7 limit 6 to yr="2004-2014" (492)
*****
```

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

This search identified 492 abstracts. Most of the abstracts from the beginning of the search period discussed mainly *Streptococcus pneumoniae* serotype distributions, antimicrobial resistance and potential effect of introducing the new 7-valent conjugate pneumococcal vaccine. The more recent abstracts primarily described the serotype coverage when moving from 7-valent to 10-valent to 13-valent pneumococcal vaccines and these abstracts were omitted. Finally a few abstracts where economic calculations in relation to introducing vaccines including varying number of subtypes, these abstracts were also omitted.

From **France**, ten abstracts were identified, describing different *surveys* performed in children, the elderly and risk groups (1,10,15,54,59–64).

From *Spain*, six abstracts were identified; three included children (65–67), two included the elderly (68,69) and one included risk groups (70). Four studies were based on surveys while two used registers.

Six abstracts from **Italy** provided coverage estimates both in children and the elderly. Both *vaccination registers* and *surveys* were described (57,71–75). In one study describing immunization strategies in the elderly it was mentioned that data on vaccination coverage was available from seven regions while from other regions only number of administered doses per year were available (74).

Two abstracts originated from **Germany** (53,76), one used *routine claims from health insurances* data, the other used vaccination cards to estimate vaccination coverage.

Among three abstracts from **Ireland**, one used a combination of questionnaire and *medical records* among diabetes patients (77), another used a *questionnaire-based* study among immunosuppressive patients to estimate vaccination coverage (78) and finally one survey was performed to estimate size of adult risk groups and vaccination coverage (79).

Two abstracts from **Portugal** investigated coverage in children using questionnaire and convenience sampling (80,81).

From the **UK**, six abstracts were identified that used *questionnaires*, *self-reports* as well as *general practitioners/primary care practice* databases. The abstracts covered primarily elderly and risk groups (82–87).

From **Switzerland** (24), **Greece** (88), **Norway** (89) and the **Netherlands** (90) one abstract from each country was identified. Norway used a national register the other three used surveys.

Among the previous **Belgium** studies identified by Lieke Van der Aa, two studies describe pneumococcal coverage (40,41). For pneumococcal vaccination coverage in adults the national Health Interview Survey is used (91). In the French community in Belgium, vaccination coverage in infants is also estimated by an *interview survey*.


	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

Table A4 in the Appendix gives an overview of the pneumococcus articles retained from the literature search.

The search result showed that in EU very few countries have published on vaccination coverage for pneumococcal disease, and amongst those only Spain, Italy, UK and Norway used registries.

### 2.2.5 Human papillomavirus (HPV)

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 3 2014> Search Strategy:

- 
1. coverage.af. (53758)
  2. uptake\$.af. (157891)
  3. 1 or 2 (210761)
  4. hpv.af. (18583)
  5. human papilloma\$.af. (20261)
  6. 4 or 5 (23804)
  7. 3 and 6 (761)
  8. (vaccin\$ or immuni\$.sh. (130192)
  9. 7 and 8 (333)

\*\*\*\*\*


In total, 333 abstracts were identified for the HPV related search. The majority of these were from the USA, followed by Australia and Canada and therefore not included in this report. In several studies the attitudes toward the vaccine or risk factors for accepting versus rejecting the vaccine were studied. In addition, several studies modelled the effect of the vaccine in relation to different coverage levels. These studies were excluded. Relatively few studies were identified where methods used for coverage estimation were presented.

From the **UK** four abstracts were identified. One article from Scotland described their HPV campaign and the use of case based data to obtain HPV coverage estimates (92) and three studies were based on different types of *surveys* (93–95).

From **France** four abstracts were identified, of which three used *reimbursement data* to calculate vaccine coverage (96–98) and one study was a survey among high school and university students (99).

From the **Netherlands** two abstracts were identified one national study (100) and one smaller study (101).

From **Germany** (102,103), **Italy** (104,105) and **Greece** (30,106) two abstracts from each country were identified and all studies used *surveys* to estimate coverage.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

In **Belgium** *reimbursement data* were used in two studies to estimate HPV coverage in Flanders (107,108). One study from **Denmark** used the *national vaccination register* to calculate HPV coverage (109). A study from **Spain** explained that HPV uptake in 4 regions is calculated based on *registers* and in the remaining regions administered doses to the target female population is used (110). Finally one study from **Switzerland** was identified using the administrative method (111).

Table A5 in the Appendix gives an overview of the HPV articles retained from the literature search.

In **Belgium**, Lieke Van der Aa identified two studies where vaccine coverage was estimated by the total number of vaccines registered in Vaccinnet (1st, 2nd and 3rd dose) as the percentage of the target group (112,113). The previously mentioned study by Theeten et al. (39) where in total 946 children and 1500 adolescents were included also covered HPV coverage. Upon the introduction of the HPV vaccine, wholesale data of the total number of HPV vaccines sold in Belgium in the first two years were analysed to obtain a theoretical coverage. These data were made available by the Intercontinental Marketing Services (IMS) Health and HPV vaccine reimbursement data from the National Institute for Health and Disability Insurance (NIHDI) (114). In addition, the National Health Interview survey of 2008 was used to estimate HPV coverage (91). A similar study was also carried out in Luxembourg and The Netherlands (115).

The literature search on HPV vaccination coverage shows that UK, the Netherlands, Denmark and Spain used national or regional registries to estimate coverage.

## 2.2.6 Influenza

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 3 2014>


Search Strategy:

```

-----
1 coverage.af. (53758)
2 uptake$.af. (157891)
3 1 or 2 (210761)
4 influenza$.af. (54075)
5 (vaccin$ or immuni$).sh. (130192)
6 3 and 4 and 5 (1365)
7 limit 6 to yr="2004-2014" (1134)
*****

```

This search identified 1134 abstracts. A large part of the abstracts were from USA, Canada, Australia and New Zealand and were omitted.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

From **France**, 37 abstracts were identified and of these 13 described national influenza vaccination coverage *surveys* (116–128) where data were obtained through telephone interviews, French sentinel GPs, refunds through the National Health Insurance, and mail-based household surveys. The remaining 24 abstracts described *surveys* among special risk groups e.g. health care personnel, individuals with underlying illness, children, pregnant women etc. using face-to-face interviews, questionnaires and telephone surveys (3–5,9,12,51,54,64,129–144).

From **Spain** 37, abstracts were extracted. Two abstracts from Navarra region used a *population-based vaccination register* to calculate vaccination coverage(145,146). In Castilla y Leon, vaccines administered were used to estimate coverage (147) and in Madrid, electronic clinical records in primary care were used (148,149). Several Spanish studies used the European Health Survey, the Madrid Regional Health Survey or the Spanish National Health Surveys to identify individuals with certain underlying diseases. Based on questionnaire data from these surveys, coverage among different risk groups were estimated (150–170). Surveys estimating vaccine uptake in health care workers were also performed (162–172)

From **Italy**, 17 abstracts were identified. Two of them described national surveys, one using telephone-based household survey (171) and one using data from a national survey of Health Conditions and Health Care Services (172). The remaining surveys included health care workers or individuals with underlying conditions using questionnaires, face to face interviews and by reviewing charts (33,57,173–185).


From **Germany**, 13 abstracts were identified of which the majority were national surveys (16,55,186–192). Most of the studies used cross-sectional telephone based household interviews. In one study, the vaccination history was obtained by vaccination cards and self-reports. A few studies were performed among special groups like healthcare workers and immunosuppressed (53,193–195).

From the **UK**, 17 abstracts were identified. Four abstracts described the use of *GP databases* to estimate influenza vaccine uptake (196–199) while one study compared survey versus register based coverage (200). In five abstracts, telephone interviews, home interviews and a postal questionnaire were used to collect data (201–205) and in seven abstracts, vaccine uptake in health care workers were analysed using primarily questionnaires (206–212).

Four abstracts from **Poland** were identified where two studies used number of administered vaccines to estimate vaccine coverage among children (213,214) another used vaccination *charts* (215) and the last study used a self-administered *survey* (216).

From **Ireland** three abstracts were found, where coverage in special risk groups were estimated using medical records and questionnaires (77–79).

In **Greece**, four out of five surveys were performed among health care workers using a questionnaire (217–220) and the last study included children with cancer (221).

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

In the **Netherlands**, pandemic influenza vaccine uptake in pregnant women was determined through an internet survey (222) while the vaccine uptake in risk groups are estimated using data from *GP-registers* (223) and *surveys* (224–226).

In **Belgium** the national Health Interview Survey is used to estimate the influenza vaccine coverage. In addition, the study by Theeten H et al. (39) also estimated influenza vaccine coverage. In the literature search two studies were identified one was a survey among GPs (227) the other was an update on vaccinations in elderly (228).

From **Sweden**, four studies were detected two national surveys (229,230) and two regional studies, one survey and one register based (231) (232).

**Switzerland** performed a questionnaire study among European travellers (233), a study among health care personnel (234) and a study among lung transplant recipients (235).

**Norway, Slovenia and Portugal** each published one study; Norway used their immunisation register *SYSVAK* to estimate coverage (236). Portugal surveyed a random sample of Portuguese families each year in 12 years (237) and Slovenia performed a questionnaire survey among physicians and dentists (238).

Finally in 12 abstracts, the influenza vaccine coverage was compared in several different countries using different survey methods (239–250). Table A6 in the Appendix gives an overview of the influenza articles retained from the literature search.

The influenza literature search showed that Spain, the UK, the Netherlands, Sweden and Norway use automated registries to estimate coverage.


### 3 Description and definition of vaccine coverage methods

At the WHO homepage:

[http://www.who.int/immunization/monitoring\\_surveillance/routine/coverage/en/](http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/) the following definitions of Administrative and Survey vaccine coverage estimation methods were found:

#### 3.1 Administrative method

In most countries "administrative coverage data" are the number of doses administered to the target population. In order to estimate vaccination coverage, this number is divided by the total estimated number of people in the target population. The target population groups vary from country to country and are dependent on the national immunization schedule in place.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### 3.2 Survey methods

Surveys aim to estimate the levels of immunization coverage at either national or sub-national levels. They aim to either establish baseline information, to provide a comparison with administrative estimates (to verify administrative coverage data), or to satisfy the demands of the partner agencies.


Although the primary objective of an immunization coverage survey is to provide a coverage estimate for selected vaccines (for infants and/or women), other information, which is usually not available through routine monitoring systems, can be collected simultaneously.

Examples of other information that can be collected are: reasons for non-immunization, proportion of administered doses that are valid, coverage by categories such as gender and socio-economic status, ownership of personal immunization records

### 3.3 Individually linked data from registries

The VENICE consortium describes computerised records as a third method to estimate coverage (251).

Several countries in Europe are building immunisation register with computerized vaccination records where records are stored with unique identifiers. In some countries linkages of vaccination information with other registers are allowed. Individually linked data do not only allow vaccination coverage estimation but allow estimation of fully vaccinated individuals within the recommended timeframe or with delay, individuals dropping out or receiving the vaccines/boosters in a wrong order etc. Table 1 gives an overview of vaccination coverage estimations methods used in Europe.


	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

**Table 1. Overview of vaccination coverage estimation methods used by the VENICE Network to estimate Diphtheria-Tetanus-Pertussis vaccination coverage**

Vaccination coverage methods			
Country	Administrative	Survey	Computer records
Austria	X		
Belgium		X	X
Bulgaria			
Cyprus		X	
Czech Republic	X		
Denmark			X
Estonia	X		
Finland		X	
France	X	X	
Germany	X	X	
Greece		X	
Hungary	X		
Iceland	X		X
Ireland			X
Italy	X	X	X
Latvia	X		
Lithuania	X		
Luxembourg		X	
Malta			X
The Netherlands			X
Norway			X
Poland	X		X
Portugal	X		
Romania	X	X	
Slovakia	X		
Slovenia	X		
Spain	X		X
Sweden	X		
United Kingdom			
<b>Total</b>	<b>17</b>	<b>9</b>	<b>10</b>

Source: Vaccination coverage assessment in EU/EEA (251)

## 4 Description of various data types

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

The Administrative method requires an estimate of how many individuals are vaccinated (or the number of vaccines distributed) in the target population. In the “Report on Vaccination Coverage Assessment in Europe” from the VENICE consortium the following numerator data are used (251).

#### 4.1 Numerator data

##### 4.1.1 Aggregated number of vaccines sold

Vaccine manufacturers have vaccine sales figures that may be used to estimate coverage. Number of vaccines sold may not be administered and therefore overestimate coverage. In addition, it is not possible to distinguish between target groups based on sales data.

##### 4.1.2 Aggregated number of vaccines distributed

This number represents vaccines distributed to e.g. general practitioners, vaccination clinics, hospitals etc. This number tends to overestimate vaccination coverage as vaccines distributed, but never administered will be included in the vaccination coverage estimate.

If a vaccine is recommended for elderly and chronic ill individuals, like the influenza vaccine, it is difficult to know how many vaccines are distributed to each group and the group specific coverage can be both under- and overestimated.


##### 4.1.3 Aggregated number of vaccines administered

When comparing vaccines distributed and vaccines administered, vaccines administered will improve the precision of the vaccine coverage estimate, as only number of vaccines given will be counted. However, if some individuals receive more than one vaccine dose the coverage will be overestimated e.g. the first time children receive the influenza vaccine they are vaccinated twice and therefore counted twice.

Using the DTP vaccine as an example, most countries recommend vaccinating children three times within the first 12 months of life. Assuming that the administered vaccines were given as recommended will overestimate the number of fully vaccinated children at 12 months of age and underestimate the number of children who has started up the DTP vaccination programme at 12 months but not received all three doses.

##### 4.1.4 Number of subjects vaccinated

This number will improve the precision of the coverage estimate as the actual number of individuals vaccinated will be known. However, this method requires that “subjects

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

vaccinated” is defined. Is a vaccinated subject one who has received e.g. one DTP injection or is a vaccinated person one who has received all injections recommended for that particular age group?

#### 4.1.5 School or day care records


This type of registration is used in some countries to estimate vaccination coverage in the childhood vaccination programme. The precision of the day care records will depend on the proportion of children in the country attending day care and how representative they are for the population of children. School records are most likely comparable over time within a country, however as the age of school start and vaccination schedules varies between countries, the coverage estimates might not be comparable between countries.

#### 4.1.6 Reimbursement data

France, Germany and Belgium (76,252–254) have published studies where reimbursement data from insurances were used to calculate coverage. The representativeness of the data depends on how common the insurance is, and if a representative subset of the population has signed up for the insurance. In addition, the coverage estimate might be underestimated if reimbursement is forgotten (255). In Denmark, the recommended childhood vaccines are free and vaccinators administering the vaccines are reimbursed by the National health insurance under the Danish Health and Medicines Authority. From 2005 to 2014, Danish vaccination coverage estimates were based on reimbursement data only using the computer linkage method.

**Table 2. Overview of numerator data used by the VENICE network to estimate DTP vaccination coverage in countries using the administrative method**

Country	Aggregated collection of number of vaccines administered	Aggregated collection of number of vaccines distributed	Number of subjects vaccinated from vaccination services or primary care physicians	Number of subjects vaccinated from school or day care records	Other
Austria	X	X	X		
Czech Republic			X		
Estonia	X		X	X	
France	X	X	X		Reimbursement data
Germany			X	X	
Hungary	X		X		
Iceland			X	X	
Ireland			X		
Italy	X		X		
Latvia	X		X		
Lithuania	X	X	X		
Poland	X		X		
Portugal	X		X	X	
Romania	X	X	X	X	
Slovakia	X		X		

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

Slovenia	X		X	
Spain	X			
Sweden				X
<b>Total</b>	<b>13</b>	<b>4</b>	<b>16</b>	<b>6</b>

Source: Report on Vaccination Coverage Assessment in EU/EEA, 2011 (251)


## 4.2 Denominator data

Denominator data are often provided from regional or national population registers. Tables 4-7 in Section 5 provide an overview of denominator data used to calculate DTP, HPV, pneumococcal and influenza vaccination coverage in the VENICE network (251). The most commonly used denominator data are population size estimates at 12 months and at 24 months, at school entry and birth cohorts. In some countries 12 months and 24 months are referred to as birth cohorts, whereas in other countries birth cohorts means children born within the same calendar year e.g. the year 2012. Using the number of children at age 12 months and/or 24 months as denominator will be a snapshot in time including children turning 12 or 24 months at the time the coverage estimation is performed. Vaccine coverage estimation at 12 and 24 months might vary between countries simply because different vaccination schedules are in place in different countries.

Birth cohorts are commonly used by countries with person identifiable computer records and a birth cohort is defined as children born within the same calendar year, which allows continuous updating of vaccination coverage for each birth cohort. As an example Denmark extracts vaccination data on all birth cohorts in March each year. All children born in 2012 were in March 2014 at least 12 months and their DTP vaccination coverage was calculated. At the same time, vaccination coverage for all children born in 2011 will be updated with vaccines given to this birth cohort between March 2013 and March 2014. When comparing vaccine coverage calculations using birth cohorts defined as calendar year of birth and calculations at 12 and 24 months of age, the 12 and 24 months method will result in vaccine coverage underestimation for older birth cohorts. This implies that these two types of estimates might not be readily comparable. Table 3 shows the differences in vaccination coverage estimates when 12 months and 12-24 months were used as denominator in Italy.

Table 3. Vaccination coverage percent (95% CI) at 12 months and between 12 and 24 months; 2006 birth cohort (based on 17 Italian regions)

Vaccines	Vaccine coverage at 12 months*	Vaccine coverage between 12 and 24 months**
Polio	80 (73.2-86.8)	96.2 (93.8-98.6)
DT	80.5 (73.8-87.1)	96.7 (94.4-99.0)
Pertussis	80.5 (73.8-87.1)	96.2 (93.8-98.6)
HBV	80.0 (73.2-86.8)	96.2 (93.8-98.6)
Hib	79.5 (72.9-86.2)	94.8 (92.1-97.4)
MMR/	-	91.0 (85.9-96.1)

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## measles

\* 3 doses of Polio, DT, Pertussis; HBV, Hib

\*\* 3 doses of Polio, DT, Pertussis; HBV, Hib; 1 dose of MMR/ measles for children age>15 months

Source: ICONA 2008, Indagine di COpertura vaccinale Nazionale nei bambini e negli adolescenti (National Survey of Vaccination coverage in children and adolescents)

Using age at school entry as denominator will increase the estimated vaccination coverage because primary childhood vaccines scheduled for the first 24 month but administered after 24 months will be included in the school entry coverage estimate. Comparison between countries is difficult as the age at school entry and vaccination schedules varies between countries.

Twelve countries report the use of other denominators and most of these are children after the age of school entry or adolescents (251).

Most countries are able to identify individuals of 60 or 65 years of age or above, which is the most common age category where influenza vaccination is recommended, however identifying cohorts of individuals with chronic diseases are in most countries difficult. Most of the studies on vaccination coverage in individuals with chronic diseases were smaller surveys where smaller group of individuals were contacted and asked about vaccine uptake, or studies using data linkage within GP health record systems.


Similarly, pregnant women to whom influenza and DTP vaccines are recommended are often difficult to identify from population registers and most studies estimating coverage in this group are based on smaller surveys.

### 4.3 Other types of data

In the Report on Vaccination coverage assessment in EU/EEA from the VENICE network and in the literature search the following survey methods were mentioned: Household surveys, telephone interviews, mail surveys, internet surveys, face to face interviews, school surveys, focus groups and other methods

The surveys identified through the literature search falls into two groups; large national surveys carried out to estimate the vaccine uptake in the general population e.g. in Germany, Belgium and France and smaller surveys performed locally or among special risk groups e.g. among: children from 1-2 larger cities, GP's in a large city or district, health care workers in one or a few hospitals, individuals with specific chronic diseases etc. Many surveys are combined e.g. mail questionnaire and telephone interview, internet questionnaire and vaccination cards/health booklet, questionnaire and face-to-face interview.

The literature search identified many smaller studies where self-administrated questionnaires were sent to e.g. health care workers and students in selected hospitals/universities. The vaccine coverage estimates obtained through these types of studies might be overestimated as individuals interested in their health often are more likely to respond to such a questionnaire


 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

and hard to reach groups may also be less likely to be vaccinated. The large national surveys are setup to be representative of the general population and often different survey methods are combined and individuals who are selected for the survey but not responding are contacted more than once (256). The setup in the large national surveys ensures vaccine coverage estimates that are representative of the general population, however it cannot be ruled out that some over- or underestimation of vaccination coverage can occur.

## 5 Overview of coverage estimation methods


### 5.1 Tables showing coverage estimation methods

These tables includes numerator, denominator, frequency of coverage estimation, time when data are available etc. and are built on the information reported by 27 out of 29 EU-countries to the “Vaccination coverage assessment in EU/EEA, 2011” by the VENICE II Consortium (251). The tables are presented as Tables 4-7.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits			
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO	28/140

**Table 4. DTP coverage estimation in children as reported to VENICE (251)**


Countries	Recommended	Method		Numerator		Denominator		Coverage estimation		Data available after (months)
		Method	Vaccine register	Type of Administrative	Type of Survey	Frequency	Immunisation level	level		
Austria	DTP	Administrative		Subjects vaccinated		All birth cohorts	Annually	Every single dose	National, regional	3
Belgium	DTP	Survey	Sub national		Household, School survey	At 24 months	Irregularly	Every single dose	Regional	1
Cyprus	DTP	Survey			Fave-to-face		Every 3 years		National	12
Czech Republic	DTP	Administrative		Subjects vaccinated		At 12 and 24 months	Annually	Full immunisation series by 24 months (incl booster)	National, regional	24
Denmark	DTP	Administrative	National + sub national	Case based on each child		All relevant birth cohorts	Annually	Every single dose	National, regional, local	6
Estonia	DTP	Administrative		Subjects vaccinated		At 12 and 24 months	Annually	Primary and full immunisation series by 24 months (incl booster)	National, local	3
Finland	DTP	Survey			Mail	At 36 months	Every 2 years			5
France	DTP	Administrative /Survey		Subjects vaccinated	household, Telephone, face-to face, School survey	At 24 months and at 6 years every six years	Annually	Primary and full immunisation series by 24 months (incl booster)	National, regional, local	24
Germany	DTP	Administrative /Survey		Subjects vaccinated	Telephone, Face-to-face, focus groups, School survey	At 24 months, and at school entry	Annually	Full immunisation series by 24 months (incl booster)	National, regional, local	16
Greece	DTP	Survey			Fave-to-face, school survey		Every 5 years	Every single dose	National	
Hungary	DTP	Administrative		Subjects vaccinated		All birth cohorts, until 7 years	Monthly	Full immunisation series by 24 months (incl booster)	National, regional, local	4
Iceland	DTP	Administrative	National + sub national	Subjects vaccinated		All birth cohorts	Annually	Every single dose	National	6
Ireland	DTP	Administrative	Sub national	Subjects vaccinated		At 12 and 24 months	Quarterly	Primary and full immunisation series by 24 months (incl booster)	National, regional, local	5
Italy	DTP	Administrative /Survey	Sub national	Subjects vaccinated	Fave-to-face	At 24 months	Annually/ Every 5 years	Full immunisation series by 24 months (incl booster)	National, regional, local	10
Latvia	DTP	Administrative		Subjects vaccinated		At 12 and 24 months, and at school entry	Monthly	Every single dose	National, regional	3
Lithuania	DTP	Administrative		Subjects vaccinated		At 12 and 24 months, and at school entry	Annually	Every single dose	National, local	3
Luxembourg	DTP	Survey			Mail		Every 5 years	Every single dose	National	
Malta	DTP		National			All birth cohorts	Quarterly	Full immunisation series by 24 months (incl booster)	National	4
Netherlands	DTP		National + sub national			At 12 and 24 months. 5 and 10 years	Annually	Primary and full immunisation series by 24 months (incl booster)	National, regional, local	6
Norway	DTP		National + sub national			At 24 months, and at school entry	Annually	Every single dose	National, regional, local	4
Poland	DTP	Administrative		Subjects vaccinated		All birth cohorts	Annually	Primary and full immunisation series by 24 months (incl booster)	National, regional	8
Portugal	DTP	Administrative	Sub national	Subjects vaccinated		At 12 and 24 months, and at school entry	Every 6 month	Primary and full immunisation series by 24 months (incl booster)	National, regional, local	2
Romania	DTP	Administrative /Survey		Subjects vaccinated	Method not specified	At 12 and 24 months	Every 6 month	Primary and full immunisation series by 24 months (incl booster)	National, local	1
Slovakia	DTP	Administrative		Subjects vaccinated		At 24 months	Annually	Primary immunisation series	National, regional, local	3
Slovenia	DTP	Administrative		Subjects vaccinated		At 12 months	Annually	Primary immunisation series	National, regional	4
Spain	DTP	Administrative	Sub national	Number of vaccines administered		At 12 months	Annually	Full immunisation series by 24 months (incl booster)	Regional	4
Sweden	DTP	Administrative		Subjects vaccinated from day care records		All birth cohorts until 35 months, and at 12-13 years	Annually	Full immunisation series by 24 months (incl booster)	National, regional, local	-4
DTP=27										

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

**Table 5. Pneumococcal conjugate vaccine (PCV 7,10,13) coverage estimation in children and special groups as reported to VENICE (251)**

Countries	Recommended	Numerator		Denominator	Frequency	Coverage estimation		Data available after (months)*		
		Method	Vaccine register			Type of Administrative	Type of Survey		Immisation level	level
Austria	PCV7_10_13 (c)	Administrative		Subjects vaccinated	All birth cohorts until age 15	Annually	Every single dose	National, regional	3	
Belgium	PCV7_10_13 (c,s)	Survey	Sub national		Household, School survey	at 24 months	Irregularly	First dose, every single dose, primary immunization series	Regional	1
Cyprus	PCV7_10_13 (c)	Survey			Fave-to-face		Every 3 years		National	12
Czech Republic	PCV7_10_13 (c,s)	Administrative		Subjects vaccinated				only one study conducted	National, regional	24
Denmark	PCV7_10_13 (c)	Administrative	National + sub national	Case based on each child	All birth cohorts as long relevant	Annually	Every single dose		National, regional	6
Estonia										
Finland	PCV7_10_13 (c)	Survey			Mail		Every 2 years			5
France	PCV7_10_13 (c)	Administrative /Survey		Subjects vaccinated	household, Telephone, face-to face, School survey	All birth cohorts, at 24 months	Annually	Primary immunisation series	National, regional, local	24
Germany	PCV7_10_13 (c,s)	Administrative /Survey		Subjects vaccinated	Telephone, Face-to-face, focus groups, School survey	at 24 months, at school entry	Annually	Primary immunisation series, incomplete immunization series	National, regional, local	16
Greece	PCV7_10_13 (c)	Survey			Fave-to-face, school survey		Every 5 years	Every single dose	National	
Hungary	PCV7_10_13 (c)	Administrative		Subjects vaccinated		All birth cohorts until 7 years, at 12, 24 months	Monthly	Primary immunisation series	National, regional, local	4
Iceland	PCV7_10_13 (c)	Administrative	National + sub national	Subjects vaccinated		All birth cohorts until 9 years	Annually	Every single dose, primary immunisation series	National	6
Ireland	PCV7_10_13	Administrative	Sub national	Subjects vaccinated		at 12, 24 months	Quarterly	Primary immunisation series	National, regional, local	5
Italy	PCV7_10_13 (c,s)	Administrative /Survey	Sub national	Subjects vaccinated		Fave-to-face	Annually/ Every 5 years		National, regional, local	11
Latvia	PCV7_10_13	Administrative		Subjects vaccinated		All birth cohorts, at 12 months	Monthly	First dose, every single dose, primary immunization series	National, regional	3
Lithuania	PCV7_10_13 (c)	Administrative		Subjects vaccinated		only newborns until 12 months				3
Luxembourg	PCV7_10_13 (c)	Survey			Mail		Every 5 years	Every single dose		
Malta			National							4
Netherlands	PCV7_10_13 (c)		National + sub national			at 12, 24 months	Annually	Full and Primary immunisation series at 2 years	National, regional, local	6
Norway	PCV7_10_13		National + sub national			at 24 months	Annually	First dose, every single dose, primary immunization series	National, regional, local	4
Poland	PCV7_10_13 (s)	Administrative		Subjects vaccinated		until 18 years		only number of doses administered in age grps	National, regional	8
Portugal										
Romania										
Slovakia	PCV7_10_13 (c)	Administrative		Subjects vaccinated		at 24 months	Annually	Primary immunisation series	National, regional, local	3
Slovenia										
Spain	PCV7_10_13 (s)	Administrative	Sub national	Number of vaccines administered						
Sweden	PCV7_10_13 (c)	Administrative		Subjects vaccinated from day care records		24-35 months	Annually	Full series	National, regional, local	.9


\* "-" indicates that data is available within the same year; c = children; s= special risk groups

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO      30/140

**Table 6. HPV coverage estimation in adolescents/special risk groups as reported to VENICE (251)**


Countries	Recommended		Numerator		Denominator	Coverage estimation			Data available after (months)	
	Adolescents	Method	Vaccine register	Type of Administrative		Type of Survey	Frequency	Immunisation level		level
Austria										
Belgium a)	HPV	Survey	Sub national		Household, School survey	at 13-14 years (planned for 2012)	Occasionally	Every single dose	Regional	1
Cyprus										
Czech Republic										
Denmark a)	HPV	Administrative	National + sub national	Case based on each child		All relevant birth cohorts	Annually	Every single dose	National, regional, local	6
Estonia										
Finland										
France	HPV	Administrative /Survey		Subjects vaccinated	household, Telephone, face-to face, School survey	at 14 years, and 15-23 years with no sexual activity		Every single dose	National	24
Germany	HPV	Survey		Number of vaccines sold	Telephone, Face-to-face, focus groups, School survey	depending on fed. State and timing of vaccination		Primary immunisation series	National	16
Greece	HPV						Occasionally			Not available
Hungary										
Iceland a)	HPV	Administrative	National + sub national	Subjects vaccinated		until 19 years	Annually	Every single dose	National	6
Ireland	HPV	Administrative/ will be in computerised registry	Sub national	Subjects vaccinated						5
Italy a)	HPV	Administrative /Survey	Sub national	Subjects vaccinated	Face-to-face	at 12 years	Every 6 months	Every single dose	National, regional, local	11
Latvia a)	HPV	Administrative		Subjects vaccinated		at 12 years	Monthly	Every single dose	National, regional	3
Lithuania										
Luxembourg	HPV					at 12-18 years		Every single dose	National	
Malta										
Netherlands	HPV		National + sub national			at 14 years		Full immunisation series	National, regional, local	6
Norway a)	HPV		National + sub national			at 16 years, for all birth cohorts (so far 1997, 1998, and 1999)	Quarterly/ annually	Every single dose	National, regional, local	4
Poland a)	HPV	Administrative		Number of doses administered		0-19 and 20+ years		Only number of doses administered	National, regional	8
Portugal a)	HPV	Administrative	Sub national	Subjects vaccinated		at 14 years	Every 6 months		National, regional, local	2
Romania										
Slovakia										
Slovenia	HPV	Administrative		Subjects vaccinated		at 11-12 years	Annually	Primary immunisation series	National, regional	
Spain a)	HPV	Administrative	Sub national	Number of vaccines administered		at 14-16 years	Annually	Primary immunisation series	Regional	5
Sweden a)	HPV	Administrative/ will be in computerised registry		Subjects vaccinated		at 12-18 years	Annually	Every single dose	National, regional, local	-9

a) Countries reporting to VENICE that the vaccine coverage is estimated using birth cohorts

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	31/140

**Table 7. Seasonal influenza vaccine coverage estimation in elderly, children, adults and special risk groups as reported to VENICE (251)(257)**


Countries	Recommended					Numerator			Denominator	Coverage estimation	
	Children	Adults	Risk groups#	Pregnant	Health care workers	Method	Type of survey	Administrative method		Frequency /availability	Level
Austria						Survey-personal interview/distribution data (industry)				other	National
Belgium		≥65 yrs	1-10	2 or 3rd trimester	all	distribution data (national)		doses distributed (national)		Annually	
Bulgaria		≥65 yrs	1-7		all	Mail survey/distribution data (national)/sales (private pharmacies)		Sales/doses distributed national		End of season	
Cyprus		≥65 yrs	1-10	2 or 3rd trimester	all						
Czech Republic		≥65 yrs	1-6, 8, 10	any trimester	all					Annually	National
Denmark		≥65 yrs	1-7, 10-11	2 or 3rd trimester, if not postpartum in risk groups	all	Registry		Claims	>64 and risk groups	Monthly	National, regional
Estonia	≥6 months-18yrs	≥18yrs, ≥65 yrs	1-10	2 or 3rd trimester	some			Subjects vaccinated		Annually	
Finland	≥6 months-3 yrs (in child immunization schedule)	≥65 yrs	1-10	any trimester	some	Survey				Annually	
France		≥65 yrs	1-6, 8, 10-11	any trimester	all	Mail survey		Claims	Annual estimate of 65+, < 65 years with chronic conditions	Weekly (only during campaign)	National
Germany		≥60 yrs (official immunization schedule)	1-8, 10	2 or 3rd trimester	all	Telephone survey/prescription data			Health care workers/occupational groups/medial condition categories	Annually	National
Greece		≥60 yrs (official immunization schedule)	1-6, 8-10	2 or 3rd trimester	all						
Hungary		≥65 yrs	1-7, 9-11	any trimester	all	prescription data		Subjects vaccinated/# of vaccines administered	Health care workers/occupational groups/medial condition categories, elderly eligible for free vaccination	every 2 months	National, regional, local
Iceland		≥60 yrs	1-10	any trimester	all	distribution data (industry and national)				Annually	National
Ireland		official ≥50 yrs (actual ≥65 yrs)	1-11	any trimester	all	Survey	comprehensive sampling	Subjects vaccinated/Claims	Some health care workers/occupational groups	other	
Italy		≥65 yrs	1-11	2 or 3rd trimester	all	computerised medical records/ registry		Subjects vaccinated	>64 years	Annually	National, regional, local
Latvia	≥6 months-2 yrs	≥65 yrs	1-6, 9		all	Registry		Subjects vaccinated/Claims/# of vaccines administered		End of season	National, regional

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	32/140

**Table 7. Seasonal influenza vaccine coverage estimation in elderly, children, adults and special risk groups as reported to VENICE (251) (257) (continued)**

Countries	Recommended					Numerator			Denominator	Coverage estimation	
	Children	Adults	Risk groups#	Pregnant	Health care workers	Method	Type of survey	Administrative method		Frequency /availability	Level
Luxembourg		≥65 yrs	1-6, 8-10	2 or 3rd trimester	all	distribution data (industry)/prescription data		Claims/doses distributed industry	>64 years	End of season	National
Malta	≥6 months-18yrs	≥55 yrs	1-7, 10		all	distribution data (national)				Annually	National
Netherlands		≥60 yrs	1-6, 10		some	computerised medical records			Medical condition categories and 60+	Annually	National
Norway		≥65 yrs	1-8, 11	2 or 3rd trimester	some	telephone survey/distribution data (national)	probability sampling	doses distributed (national)		End of season	National
Poland	≥6 months-18yrs	≥55 yrs	1-11	any trimester	all	Distribution data (national)		Subjects vaccinated		Annually	National, regional
Portugal		≥65 yrs	1-11	2 or 3rd trimester	some	Registry/Telephone/distribution data (industry and national)/sales (private pharmacies)	probability sampling	Subjects vaccinated /sales /Doses distributed national & Industry/# of vaccines administered	Health care workers/ occupational groups	End of season	National, regional
Romania		≥65 yrs	1-8, 11	any trimester	all			Subjects vaccinated/# of vaccines administered	Health care workers/occupational groups/medial condition categories	End of season	
Slovakia	≥6 months-12 yrs	≥59 yrs	1-5, 7,10		some	distribution data (industry and national)/prescription data		Subjects vaccinated/doses distributed industry		Annually	National
Slovenia	≥6 months-2 yrs		1-10	any trimester	all	Survey		Subjects vaccinated	Health care workers/occupational groups/medial condition categories/>65 years	End of season	National, regional
Spain		≥65 yrs	1-11	any trimester	all	computerised medical records/ registry			Health care workers/ occupational groups	Annually	Regional
Sweden		≥65 yrs	1-8, 10	any trimester, not vaccinated with pandamrix2009		computerised medical records/ registry/mail survey		Subjects vaccinated/# of vaccines administered		Annually	National, regional
UK (Eng, Wales, N Ir and SC)		≥65 yrs	1-8, 10	any trimester	all	Eng/Wales/SC= computerised medical records; N Ir =survey		Eng=Subjects vaccinated; N Ir/Sc =Claims	Eng/N Ir/wales= Health care workers/ occupational groups; Eng/Wales/SC=medical condition categories	N Ir= Monthly Eng=weekly	National, regional local

#: 1=Chronic pulmonary (asthma included), 2=Cardiovascular (hypertension excluded), 3=Renal, 4=Haematologic/metabolic (diabetes mellitus included), 5=Immunosuppressive (asplenia/splenic dysfunction organ trasplantation, cancer included ; AIDS/HIV excluded), 6=HIV/AIDS, 7=Hepatic, 8=Chronic neurologic/neurotransmitter disorders, 9=Long term aspirin use (up to 18 yrs old), 10=conditions affecting respiratory function, 11=Morbid obesity (BMI ≥40)

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## 6. Electronic registration of vaccines

### 6.1 Sales of vaccines: wholesales to pharmacies, sales to vaccination clinics and GPs


The literature search identified one publication where vaccines distributed were used as one method to estimate DTP coverage. In another European study HPV vaccine sales data in 22 European countries were used to calculate 1) yearly rate of PVC7 doses sold per 100 live births and 2) completed vaccination courses per 100 live births (258).

Upon the introduction of the HPV vaccine in Belgium, wholesale data on the total number of HPV vaccines sold in the first two years that the vaccine was made available, was analysed to obtain a theoretical coverage. Data were made available by the Intercontinental Marketing Services (IMS) Health and HPV vaccine reimbursement data from the National Institute for Health and Disability Insurance (NIHDI) (114). A similar study was carried out in Belgium, Luxembourg and The Netherlands and here sales statistics were obtained from Intercontinental Marketing Services to calculate the theoretical coverage in the three countries (115). In one study from the VENICE consortium, the number of seasonal influenza vaccine doses in 2007-2008 in member states per 10,000 population at risk was calculated using EU country specific estimates of the elderly population and clinical risk groups. Although not all vaccines were given to these two groups of people this is a crude way of analysing supply against need and making comparison between EU countries (259). In addition, Cyprus and Portugal use sales data to estimate influenza vaccine coverage (Table 7).

### 6.2 Prescription databases, Health records from GPs, hospitals or well-visit clinics

Vaccines that are recommended but not part of the national vaccination programme are not reimbursed and therefore often not registered. In Denmark, the pneumococcal vaccines are recommended to elderly people but only those pneumococcal vaccines sold through pharmacies are registered in a prescription database. Many vaccines are delivered exclusively from Statens Serum Institut to the vaccinator and therefore not registered in a prescription database (260).

In England, GP registers are often used to evaluate selective vaccination programmes for adults e.g. seasonal influenza and pneumococcal vaccines (261). In addition, some European countries have GPs sentinel networks that register influenza like illness and seasonal influenza vaccine uptake in the electronic health records, and these data can be used to estimate vaccination coverage in those groups.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## 6.3 Vaccination registries

Some countries have started to build electronic vaccine registers where GPs and vaccination clinics etc. register vaccines given to each individual. These types of records provide unique opportunities to perform benefit-risk studies.


### 6.3.1 *Denmark*

Since the year 2000 Denmark has had a national childhood vaccination database with information on all vaccinations administered to children below the age of 18 years and recommended by the national childhood vaccination programme (260). Each person in Denmark has a civil registration number and all vaccines given must be registered together with the civil registration number. The Danish childhood vaccination database consists of electronically reported data derived from a state-managed administrative register on services offered by GPs, who are reimbursed from the national health insurance system when they administer vaccines recommended by the Danish childhood vaccination programme. In this database there is no product name or batch number, data are entered with 3 months delay and vaccines given outside the childhood vaccination programme are not included.

In 2008, the Danish government decided to establish a national vaccination register (Danish vaccination Register (DDV)) where the missing information mentioned above will be recorded.

1. Vaccines are registered real-time
2. Mandatory reporting of all vaccines given
3. Date of vaccination
4. Type of vaccine
5. Personal identifier of individuals vaccinated
6. Personal identifier of vaccinator
7. Product name
8. ATC code
9. Dosage
10. Batch number
11. Organisation of vaccinator

DDV will be running from January 2015 and data from the national childhood vaccination database from 1996 has been imported into DDV. Some of the vaccines that are not part of the childhood vaccination programme are prescribed by GPs to the individuals who are vaccinated. These prescriptions will also be imported to DDV.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### 6.3.2 Norway

The Norwegian immunisation register SYSVAK is a national electronic immunisation register that became nationwide in 1995 (262). The original aim was to register all vaccination in the Childhood immunisation programme. In 2009 the SYSVAK was expanded and now it includes HPV vaccinations (including those given outside the vaccination programme), vaccinations against all other vaccine preventable diseases and travel vaccines. Health professionals are obliged to notify all vaccination in children and adults to SYSVAK. The immunisations within the childhood vaccination programme are provided by public health nurses and general practitioners usually play no role. All vaccines are free of charge. In SYSVAK the following information is available:

1. Personal identification number and name of vaccine
2. Specific code and name of each vaccine
3. Batch number of the vaccine
4. Date of vaccination for each dose
5. Date of notification to SYSVAK for each dose
6. Name and location of vaccinating unit (health clinic, GP, etc)


### 6.3.3 Sweden


From January 2013, all vaccines given in the national childhood vaccination programme are registered in the Swedish national vaccination register. Registration of vaccines is nationwide and mandatory. There are about 100 000 children in a birth cohort in Sweden and the vaccination coverage is almost 100%, with some exceptions. Vaccinations against the following infections are given in the child vaccination program: diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b, pneumococcal disease, measles, mumps, rubella and HPV-infection (girls 10-12 years). In the near future hepatitis B and rotavirus vaccines will probably also be included.

The following variables are registered:

- 1) Personal identification number
- 2) Date of vaccination
- 3) Name of vaccine
- 4) Batch number
- 5) Health care provider responsible for vaccination

The dose number is not yet included as a variable. This is currently being discussed and has been asked for by the Public Health Agency of Sweden.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### 6.3.4 SVEVAC

Between 2006 and 2013, HPV-vaccination was registered in a vaccination register called SVEVAC. HPV vaccination was not included in the vaccination program until January 2012 and has been registered in SVEVAC until January 2013. All the registrations made in SVEVAC up until 2013 can be individually linked and used for research purposes.

SVEVAC is a voluntary register and is today used by 10 000 health care users in Sweden for vaccinations outside the vaccination program e.g. HPV-vaccination catch-up (13-17 years) and influenza. Currently 2.3 million people are in the register with 62 million vaccinations registered. In July 2013 the register turned into a medical chart system, which means, legally, that we cannot extract individual data for research purposes. However, it is possible to extract aggregated data.

Since this is not a pure vaccination register other information such as adverse reactions and some disease history may be available as well.

### 6.3.5 Iceland


A central registry of vaccinations has been available in Iceland since 2007 and contains information on all childhood vaccinations as well as information on most adult and travellers vaccinations from 2002 (Thor Gudnason, Centre for Health Security and Communicable Disease Control, personal communication). Before 2007, information on vaccinations was only obtainable at the sites where they were carried out.

The electronic immunization registry is an electronic real time interactive central database which contains information on:

- Personal identifiers of the vaccinees
- Date and site of vaccination
- ATC/HL7 number and brand names of the vaccines
- Individual refusal of vaccinations

The immunization registry is currently being used to measure vaccination coverage, evaluate programs at different sites and to obtain lists of un- and partially vaccinated children. The potential utilization of the registry includes estimation of vaccine effectiveness, monitoring adverse effects, refusal of vaccinations and cost, and opportunities for individuals to check their own immunization status on-line. The data can be linked to other databases with person identifiable data

### 6.3.6 Finland

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

Since 2010, vaccination records have been part of the data content of the outpatient primary health register and since 2012 all Finish health care centers are obliged to deliver individual vaccination records electronically and the database is updated daily, however the reporting delay from the health care centers varies (Ulrike Baum, National Institute for Health and Welfare personal communication). The following information is available in the register:

1. Personal identification code
2. Batch number and/or trade name
3. Date of vaccination
4. Municipality administrating the vaccine

### 6.3.7 The Netherlands

The Dutch immunisation register Praeventis is an electronic national immunisation register that was implemented in 2005 (263). This register is linked to the population register and produce letters of invitation for the national immunisation programme. In addition, Praeventis has an algorithm to validate the administered vaccines. In this register all children are registered with a unique client number and these data can be linked with other existing databases. When the child is vaccinated the following information is entered into Praeventis:


- 1) Unique client number
- 2) Vaccine characteristics
- 3) Dose
- 4) Data of administration
- 5) Executive organisation
- 6) Objections to vaccination

Praeventis includes both vaccinated and unvaccinated individuals and participants of studies such as questionnaire studies, vaccination trials, focus group studies and vaccine effectiveness studies can be recruited through the immunisation register. These individuals are asked by post whether they are willing to participate in a specific study.

Praeventis only includes vaccines that are part of the National Immunisation Programme which means that seasonal influenza vaccines, travel vaccines and all other vaccines administrated outside the National Immunisation Programme are not registered.

### 6.3.8 Belgium

Child and Family are public health service centres in Flanders offering preventive health care for all children under the age of three years. Since 1999, an infant vaccination database implemented by Child and Family was available. Vaccinnet was established in 2004-2005 and

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

build upon the database from 1999. Vaccinnet is an online order system for any vaccines freely provided to vaccinators by the Flemish authorities. Since 2005, School Health Services record all newly administered vaccinations in Vaccinnet. The database is linked to the resident registers of Flanders and the Capital Region of Brussels. Since 2006, the system is accessible for all GPs and paediatricians (264)

The use of Vaccinnet has increased and a study was set up comparing Vaccinnet and an immunisation survey to investigate whether Vaccinnet may serve as an immunisation information system to provide estimates of coverage and timeliness of recommended infant vaccinations in Flanders (264). According to this study, Vaccinnet underestimates the vaccination coverage rates compared to the survey study (mean difference 7.7%, range 4.2–12.7%). It is the objective of the Flemish government that in 2015, all vaccinators order vaccines sponsored by the Flemish government by Vaccinnet (Action Plan Vaccination 2012-2020, Flemish Agency for Care and Health), which should increase the completeness of the register. Vaccines given to older age groups (adolescents and adults) can be registered by physicians in Vaccinnet, but this is currently only done rarely. Vaccines that cannot be ordered through Vaccinnet (e.g. for rotavirus, which is not reimbursed by the Flemish government), can still be registered in Vaccinnet (264).


In 2014, a similar online vaccine ordering system, e-vax, was introduced in Walloon and Brussels by the French Community.

Vaccinnet and e-vax contains the following information:

- 1) PatientID
- 2) Date of birth
- 3) Sex
- 4) Administrator
- 5) Vaccination date
- 6) Registration date
- 7) Lot-number
- 8) Brand name of vaccine (Commercial name)
- 9) Diseases against which vaccine provides protection
- 10) Manufacturer
- 11) Type of information: administered vaccine (administration)
- 12) Facility where vaccine was administered
- 13) Also possibility to register side effects (open field)

### 6.3.9 England

Child Health Systems (CHISs) are computerised clinical record systems, which support a range of health activities for children including immunisation and screening (260). There are a

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


number of different providers of CHISs in England. The systems are managed by child health departments in each local area. Data on vaccines administered in England are currently recorded on two computerised systems, general practitioners databases (along with other GP data) which capture vaccinations given by general practices and other vaccinations where this information is passed to the GP, and population based child health information systems (CHISs) which have childhood vaccinations recorded. Similar systems operate in Scotland, Wales and Northern Ireland. CHISs are generally used to estimate vaccine coverage for the routine childhood immunisation programme while the GP databases are often used to evaluate selective vaccination programmes for adults (e.g. seasonal influenza and pneumococcal vaccines).

CHISs are managed by child health departments in each local area (Primary Care Trusts (PCTs)). The PCT responsible population is defined as all children registered with a GP belonging to that particular PCT plus children not belonging to a GP and who are resident within the PCTs geographical area. This is the denominator for each CHIS used for vaccine coverage estimation in the childhood vaccination programme. The nominator is the number of vaccines administered. Information on vaccine coverage is requested for all children in the PCT population who reach the first, second and fifth birthday during a particular quarter. The extracted data are aggregated and include number of eligible children in each cohort and numbers and proportions vaccinated for all routine vaccinations offered according to the national immunisation schedule. Studies have shown 1% to 9% underestimation of the true uptake (261).

### 6.3.10 Ireland

There are eight Primary Childhood immunisation registry which cover the four regions in Ireland (Suzanne Cotter, HSE Health Protection Surveillance Centre, personal communication). The current versions of these systems have been in existence since the 2008 and the following information is available from the immunisation registers:

1. Name and address of the vaccinated person
2. Date of birth
3. Date of vaccination
4. Gender
5. Social security number
6. Type of vaccine
7. Vaccine trade name
8. Vaccine dose number
9. Vaccine lot number
10. Vaccine provider

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

In recent years, during the influenza pandemic and in response to the pandemic influenza vaccination programme, a National Pandemic System was developed to capture the vaccines administered in mass vaccination clinics and schools as part of the pandemic vaccination response. Pandemic vaccinations given in the Primary Care setting were captured on a web browser provided by the Primary Care Reimbursement Service. The Eastern Regional Information and Communications Department developed this IT system in collaboration with a developer.

The National Pandemic System was subsequently tailored for use as a national system to collect data on HPV vaccines administered in the school programme to girls and to report on this uptake. This system has now been developed further and has been renamed as the School Immunisation system to cater for all school based immunisations programmes and from 2015/2016 Academic year will be used to collect other data relating to HPV, Tdap, Men C in second level schools and MMR and 4 in 1 vaccination in the Primary School settings.

The following information is available from the School Immunisation System:


1. Name and address of the vaccinated person
2. Date of birth
3. Date of vaccination
4. Gender
5. Type of vaccine
6. Vaccine name
7. Vaccine dose
8. Vaccine Batch number
9. Vaccine Manufacturer

### 6.3.11 Spain

Some regions and cities in Spain have a centralised immunisation register (265). Regional centralised registers in Spain include Murcia, Galicia, Valencia, la Rioja and Andalucia, and city registers include Barcelona and Salamanca. These registers are not connected to each other. Elsewhere in Spain, vaccines administered are recorded on individual case reports in primary health care. There is no centralisation of data at the country level. Most regions use official population figures to calculate coverage, except in la Rioja and Murcia which have their own population database.

#### Murcia region (Spain) (265)

The computerised vaccination register in Murcia was set up in 1991. The register has evolved over time and currently all vaccines administered in the region are recorded, both from private and public operator, vaccines given during childhood and to adults and also vaccines outside

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

the official vaccination scheme. The vaccination register is linked to the population database, which allows real-time update of the population. Each person has a regional personal identification code. The register records:

- 1) Regional personal identification code
- 2) Date the vaccine was administered
- 3) Vaccination post
- 4) The product administered
- 5) Dose order in case it is part of a vaccination series
- 6) Manufacturer and batch number
- 7) Indication for vaccination

#### Navarra (266)

All Navarre residents are at birth registered in the healthcare computerised system and people who change address to Navarre region are registered. From 2000 to 2004 computerised medical records were implemented throughout the Navarre health service both in hospitals and primary care.

Whenever health professionals administer a dose of vaccine the following must be registered:


- 1) Type of vaccine
- 2) Dose number
- 3) Brand and batch number
- 4) Date of administration
- 5) The person who administers the vaccine
- 6) Possible incidents

The data can be linked to other databases

#### **6.3.12 Portugal**

A Computerised Vaccination Registry System was gradually implemented throughout the country since the year 2000 (Teresa Fernandes, Directorate of Disease Prevention and Health Promotion, personal communication). All local health centres already have access to this system, which is nested in the Health Centres' registry system. All the individual vaccines administered at the health centres (vaccines offered or from the private market) are registered in the system. Characteristics of this system:

1. Vaccines are registered real-time
2. Mandatory reporting of all vaccines administered
3. Date of vaccination
4. Personal identifier of individuals vaccinated

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

5. Personal identifier of vaccinator
6. Type of vaccine
7. Product name
8. Dosage
9. Batch number
10. Service of vaccinator

This system allows:

- Vaccine stock management – at local level,
- Individual alerts if delayed vaccine schedule at local level
- Individual calls for vaccination if delayed, at local level
- Automatic calculation of vaccine coverage in real time, at local and regional level

An upgrade of this system is being developed with the following major improvements:

- Web based
- Will be available at local, regional and national level
- Will be linked to the national patient registry


### 6.3.13 Italy

Childhood vaccination services in Italy are usually provided by vaccination centres in local health Authority (LHAs) (267). Italy has 157 LHAs in 21 regions. All LHAs in Italy estimate coverage using the administrative method with number of vaccinated people as numerator and the local population obtained from the administrative database or from the health system database as denominator. The Ministry of Health collects annual data from all regions on number of vaccines administered for most vaccines. These data are collected on paper.

In July 2011, a survey was carried out including all 21 regions and 157 LHAs, regarding level of computerisation of immunisation registers. Fifteen regions and 130 LHAs are fully computerised. In eight out of 15 regions the LHAs uses the same software and in seven regions the LHAs use different software. Individual data are accessible in six of the 15 regions, in the remaining 9 regions individual data are stored at LHA level but only aggregated data on vaccine coverage are extracted and forwarded to the region.

Five regions are partly computerised and the proportion of LHAs using computers varies from 25 to 92%. One region does not use computers

While the types of register varies by region, whether paper or electronic, the following basic information is always collected:

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

1. Date of vaccination
2. dose number
3. Brand
4. Vaccine lot

#### Lombardia (Anna Cantarutti, personal communication)

All LHAs have their own computerized immunization registry and can estimate local vaccine coverage for the birth cohorts from 1990 onwards. Each LHA sends the immunization registry to a central regional repository where regional coverage is estimated; these data are available to healthcare professionals on the regional website. The same data are included in the individual electronic health records.

Numerator data:

Case based information on subjects vaccinated.

Denominator data:

The denominator is derived from the regional demographic registry. In particular, the denominator is the sum of all the residents contained in the registry with the exclusion of: children temporarily returned to the country of origin, the nomads, the homeless and the non-traceable (adjusted coverage).

#### Electronic registration

Electronic registration of vaccines was introduced in Lombardia in 2006, but includes data on vaccinations from the 1990 birth cohort onwards. Different software are used within the region by LHAs, but everyone has an add-in, called “GEV” (Gestione = management, Eventi = events, Vaccinali = vaccination), that sends data to the regional Directorate of Health. Each software is linked with the regional demographic registry, through which patients are identified. Each patient has a personal page where the vaccinations received and missing are registered. The software provides information about when the vaccine/booster was administered, the marketing authorization number of the vaccine and the batch number.


#### Veneto (Anna Cantarutti, personal communication)

Numerator data:

Case based information on subjects vaccinated.

Denominator data:

The denominator is derived from the regional demographic registry. In particular, the denominator is the sum of all the residents contained in the registry with the exclusion of: children temporarily returned to the country of origin, the nomads, the homeless and the non-traceable (adjusted coverage).

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### 6.3.14 Slovenia

The following description of the Slovenian immunization register was identified at <http://www.folkhalsomyndigheten.se/documents/publicerat-material/konferensdokumentation/ECIIS-2010/poster-iis-slovenia-eciis-2010.pdf>


The collection and processing of data on compulsory immunisation for preschool children in Slovenia was supported by the CEPI\_2000 software until 2009. Because the outdated software no longer enabled the distribution of information on conscripts nor the data on implemented vaccinations, the National Institute of Public Health launched an initiative in 2009 for the revision. The new system will be called eRCO (electronic Register of Vaccinated Persons), this central database will collect data on all vaccinations that were carried out, as well as on adverse events and immunisation exemptions.

Based on the survey on computerised immunisation registries in Europe the following information is available in the immunisation register in Slovenia (268):


1. Name and address of the vaccinated person
2. Unique identifier
3. Date of birth
4. Date of vaccination
5. Gender
6. Social security number
7. Type of vaccine
8. Vaccine trade name
9. Vaccine dose number
10. Vaccine lot number
11. Vaccine provider
12. Anatomical site of vaccination

### 6.3.15 Malta

Malta uses a national electronic immunisation database (Victoria Farrugia, Sant'Angelo, Floriana Health Centre, personal communication). This was introduced in 1998 using a system called FoxPro. In 2009, all data on FoxPro was transferred to a new program created specifically for the National Immunisation Service. The Maltese National immunisation database consists of electronically reported data derived from direct registration of vaccinations administered at State-run clinics and schools. GPs specialists working in the private sector are obliged to report all vaccinations administered by them. These vaccinations are then registered in the system. Reports are registered as soon as they are received at the National Immunisation Service. All vaccines are registered, including those that are not on the

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

National Immunisation Schedule and all vaccines given to adults. The following details are recorded in the Database:

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


- 1) Vaccines registered real-time
- 2) Vaccines administered in the private sector registered on receipt of report from GP or specialist
- 3) Date of vaccination
- 4) Type of vaccine
- 5) Personal identifier of individuals vaccinated
- 6) Personal identifier of vaccinator
- 7) Product name
- 8) Dosage
- 9) Batch number

The program has the capacity to generate reminders for subsequent scheduled vaccines and these can then be mailed to individuals. Reports and coverage rates can also be extracted from the database.

### 6.3.16 Other European countries

For Portugal we identified the following description. Since 2000 a computerised vaccination registry system is being gradually implemented throughout the country. Calculation of vaccine coverage real-time on a national basis will not be possible until all health care centres are connected [http://venice.cineca.org/documents/portugal\\_ip.pdf](http://venice.cineca.org/documents/portugal_ip.pdf).

A Siedler et al (256) has described the vaccine coverage estimation in Germany where immunisation registers are absent, however the article does mention one state where all vaccinations of children up to 7 years must be reported to the local public health service by law. This might be what the VENICE report regards as a subnational immunisation register.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## 7. Discussion of results


### 7.1 In general

The literature search only identified vaccine coverage data and methods published in peer-reviewed papers for which vaccine coverage estimation is one of the objectives of the article. The literature search did not capture vaccine coverage estimates published in national reports or papers where the description of coverage was a minor part of a scientific study and only described in the material and method section. As indicated by Tables A1-A6 in the Appendix, the majority of published coverage data in Europe are from different types of survey. Countries using the administrative method rarely publish these data in scientific journals. Very few peer-review papers used vaccine registers for coverage estimation, however many countries are still developing national vaccination registers and it is likely that in the future more articles will be built on computerised vaccination records.

Vaccine coverage estimates may serve many different purposes. When public health authorities want to plan future action and campaigns to increase timely vaccine uptake in e.g. children and adolescents, then vaccine coverage estimates obtained at the time the vaccine is recommended is important. However in benefit-risk studies it is important to get a precise estimate of how many were actually exposed to the vaccine, which means that vaccine coverage estimates obtained some time after the vaccine was recommend is more valuable as individuals who receive the vaccine later than recommended will also be included.

### 7.2 How comparable are vaccine coverage estimates between countries

For DTP, 19 countries participating in the VENICE network have reported using the administrative method and of these 17 countries used subjects vaccinated (Table 4). As discussed earlier in this report, it is important to define a subject vaccinated; however, as WHO requires that countries report DTP1 and DTP3 coverage both these figures are available in the different countries. When comparing the choice of denominator for DTP coverage estimation, more variation is observed with countries using all birth cohorts, at 12 and 24 months, only 12 month or only 24 months. As discussed earlier, countries using birth cohorts defined as children born in the same calendar year are able to continuously update their coverage estimates, which allows vaccines received later than recommended by the national vaccine schedule to be included in the vaccine coverage estimate. The birth cohort method will most likely produce coverage estimates that are higher than the 12 months and 24 months denominator methods, as the fixed month method does not allow vaccines received after 12 and 24 months to be included in the coverage estimate. This difference is illustrated in Table 3 where childhood vaccination coverage was estimated in Italy at 12 months and between 12 and 24 months, which resulted in at least 15 percentage-points difference in vaccine coverage for all childhood vaccines.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

For the pneumococcal conjugate vaccine, most countries report that they use the administrative method to estimate coverage and 12 months and 24 months are the most commonly used denominators (Table 5). However, some countries are combining denominators (e.g. all birth cohorts, at 24 months) and here it is not clear if the denominator is children born within the same calendar year and at least 24 months or the denominator is children at the time they are 24 months.


Comparing childhood vaccines schedules between European countries (Table A7, A8, A9 and A10) and <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx> indicate that in the majority of European countries primary vaccines are given within the first 24 months and, in order to obtain the most comparable vaccine coverage estimates for benefit-risk analyses, vaccine coverage calculated at 24 months should be preferred and not at 12 months. For benefit-risk analyses, an additional coverage estimation at e.g. 30 months would improve the comparability between the birth cohort method and the fixed-month method.

Using birth cohorts as the denominator does not guarantee that coverage estimates can be compared between countries. E.g. Denmark estimates vaccine coverage in March each year and in 2014 DTP1 and DTP2 coverage was based on the 2012 cohort while DTP3 coverage was based on the 2011 cohort which allows children who receives the DTP vaccine later than recommended to be included in the coverage estimate. However other countries might use other assumptions which can produce different results e.g. in the Netherlands at the 2<sup>nd</sup> birthday of the child it is determined if vaccination according to age was completed or not and this information is combined for all children of one birth cohort.

Following the primary vaccinations given before 24 months of age, a second round of childhood vaccines are given at approximately 4-6 years of age. Several countries use school entry as the denominator to calculate vaccine coverage. In order to compare these estimates between countries it is important that age of school entry is provided and compared with national recommendations. When age at school entry is provided it is most likely possible to compare these estimates with the birth cohort estimates obtained from the same age groups.

Germany, Belgium and France run large national surveys where a representative subsample of the population is contacted and information about vaccinations are collected (256,269,91). It is difficult to say how comparable the survey and the administrative methods are, however if the sampling scheme is well planned and different survey methods are combined it is reasonable to assume that such surveys produce results that are comparable to those provided by administrative methods based on vaccinations registered at individual level.

According to European vaccination schedules available at the ECDC homepage (Appendix Table A11) 25 countries recommend HPV vaccination. In most countries this vaccine is recommended at 12 years of age. A few countries start vaccinating before age 12 and some countries do not recommend this vaccine until 18 years of age. Sixteen countries have reported to VENICE that HPV coverage estimation is performed and of these 14 do so annually or more frequently. Most countries use the administrative method, a few countries

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

use a combination of the administrative and the survey methods and two countries use only the survey method. Several countries has reported to VENICE that the denominator is adolescent birth cohorts (Table 6), however the same countries also write that the coverage estimation is done at e.g. 12 years or 14 years and it is not clear whether the denominator is adolescents turning 12 or 14 years or adolescents born within the same calendar year and they are at least 12 or 14 years at the time of coverage estimation. As discussed for DTP, HPV coverage estimation will most likely be lower in countries using the time an adolescent reaches a certain age compared with countries defining birth cohorts by calendar year. To obtain the most comparable results coverage estimation should be performed as late as possible e.g. around 15 years of age.

Table 7 presents influenza vaccine coverage estimation methods and risk groups recommended vaccinated against influenza. Many countries indicate that they combine the administrative and the survey method. For the administrative coverage method subjects vaccinated, doses administered and insurance claims data are often used as the numerator. As denominator health care workers, occupational groups, individuals with underlying conditions and elderly are used, which correspond to the risk groups recommended vaccinated in most countries. Most countries recommend that pregnant women are vaccinated; however no countries mention pregnant women as a denominator category.


## 8 Conclusions and recommendations

### *Conclusions*

Based on the literature search and the work done by the VENICE network, it is clear that no standardised ways to estimate or report vaccine coverage exist in Europe.

WHO receives yearly vaccine coverage estimates from all over the world, but they do not take into account that different vaccination coverage methods are used. As an example, the DTP1 coverage in Denmark in 2014 was based on data from the 2012 cohort while DTP3 coverage was based on the 2011 cohort and the country specific vaccination coverage's are compared without descriptions of the coverage estimation methods used. Very few reports address limitations and uncertainties in the reported data, which may provide a false sense of certainty.

Vaccine schedules do vary between countries and the different schedules can make coverage estimation difficult, however there are certain age groups where very few countries recommend vaccinations e.g. from 2-4 years and from 8-10 years. From a benefit-risk point of view, an additional coverage estimation should be performed for the age groups 2-4 years and 8-10 years to obtain more comparable estimates.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	51/140

In many countries, it is difficult to identify individuals where vaccination is recommended (e.g. pregnant women and persons with underlying illness) which can imply that coverage estimations for these groups are difficult.

The aim of the ADVANCE project is to perform timely benefit-risk analyses of licenced vaccines, i.e. mainly related to the objectives 2 to 4 mentioned in the introduction. Recommendations should be targeted towards these aims. Therefore it is essential to know with a high degree of certainty the proportion of individuals in the population exposed to the vaccines rather than the exact coverage at a young age, or the waiting time to obtain a specific vaccination coverage. This means that the vaccine coverage should preferably be calculated with a considerable delay after the planned vaccination schedule. For most countries this means for primary vaccines at 24 to 36 months and not at 12 months. For booster doses, uptake at 8-10 years may be more appropriate than at 6 years or at school entry.

### *Recommendations*

Where comparable vaccination coverage estimates are important:


The variation introduced due to different methods and between countries due to different vaccination schedules can to some extent be reduced if vaccination coverage estimation is postponed until the age groups 2-4 years and 8-10 years. Very few countries are recommending vaccinations during these time periods, which allow children being vaccinated late to be included in the vaccination coverage estimates.

Where vaccination coverage estimates are needed as fast as possible.

Several European countries have or are building electronic vaccination registers where vaccination data are person identifiable and available as soon as the vaccination is entered into the register. These registers allow continuous vaccine coverage estimation that is not bound to a specific age in months. As the child's age in months will be available at time of vaccination, Kaplan Meier curves or other statistical tools can be used to estimate the optimal age to estimate vaccination coverage for each vaccine dose across countries when both timeliness and vaccine exposure should be taken into account. The identified optimal age to estimate vaccine coverage should be compared with the country specific immunisation schedules available from ECDC homepage.


In case electronic vaccine registers are not available and timely estimates are not available.

WHO receives vaccination coverage estimates yearly from all countries and these estimates could be an alternative vaccine coverage source.


 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	61/140


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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
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## **PART II: BENEFITS OF VACCINES AND VACCINATION PROGRAMMES**


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With contributions by Marianne van der Sande, Wim van der Hoek, Mirjam Knol, Vincent Bauchau, Denis Macina, Nick Andrews, Hanna Nohynek, Emil Cochina, Kaatje Bollaerts, Thomas Verstraeten, Katherine Donegan, Clarisse Demont and Silvia Taylor

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## Abbreviations

AR	Attack rate
EIA	Enzyme immune assay
Hib	Haemophilus influenzae
HPV	Human papilloma virus
i-MOVE	Influenza-Monitoring vaccine effectiveness
OR	Odds ratio
PBRER	Periodic benefit-risk evaluation report
PCR	Polymerase chain reaction
PCV	Proportion of cases vaccinated
PH	Public health
PPV	Proportion of the population vaccinated
RCT	Randomised controlled trial
RR	Relative risk
SAR	Secondary attack rate
TND	Test negative design
VE	Vaccine effectiveness
VPD	Vaccine preventable disease

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
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## 1. Introduction

Benefits of vaccination and vaccination programmes are assessed pre- and post-implementation of vaccination recommendations and programmes. Stakeholders involved in this include public health, regulatory authorities, vaccine manufacturers and academia. We divide the term ‘benefits’ in two areas: vaccine effectiveness and impact of vaccination. The methods to assess these are separated into epidemiological methods and methods based on mathematical modelling. Our assessment of methods is carried out focussing on their performance to deliver evidence for policy decisions about the use of vaccines.

## 2. Perspectives on benefit assessment

### 2.1 The perspective of public health authorities.

The first rationale for public health (PH) authorities to monitor vaccine benefits is to identify (emerging) problems with the vaccine, the vaccination programme or changes in the disease epidemiology which affect vaccine effectiveness (VE). A low VE may necessitate changes in the vaccine or vaccine schedule. An example is the relatively low effectiveness of Hib vaccine found in the UK in 2002, which led to a booster dose of Hib vaccine introduced with a catch-up campaign (1).


PH authorities are also concerned with monitoring the impact of vaccination programmes in order to justify their existence, support the associated costs and to identify opportunities for improvement.

### 2.2 The perspective of regulators.

From the regulatory agency’s point of view, the broad aim is to ensure that sufficient data are available to support the ability of the vaccine to provide protection in accordance with the proposed/authorised indication. The key data to be considered in benefit evaluation and within the regulatory decision-making process will relate to the potential direct benefit data (e.g. efficacy and/or immunogenicity data), optimal dose schedule(s), longevity of immunity and need for boosters. However, effectiveness data, including data on indirect benefits, will also inform evaluation of benefits and the protection offered by a vaccine and may also be requested by regulators. This is particularly the case if it was not feasible to estimate the protective efficacy of a vaccine pre-authorisation and/or there are no established immunological correlates of protection. In such cases, it may be necessary for manufacturers to obtain effectiveness data in the post-authorisation period to inform continuous risk-benefit evaluation in the authorised indication. Furthermore, there may be situations when the potential impact of use of a particular vaccine, via a national vaccination programme, on the epidemiology of the vaccine preventable infection(s) needs to be addressed in the post-authorisation period.

### 2.3 The vaccine manufacturers’ perspective.

The vaccine manufacturer may approach benefit-risk evaluation from two perspectives depending on the objectives and context of the evaluation.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

In the context of regulatory required monitoring of benefit-risk, such as for PBRERs (periodic benefit-risk evaluation reports), the primary perspective for monitoring of both benefits and risks of the vaccine will be limited by the approved indication claims for the vaccine. Within these limits, the perspective of the monitoring will focus mainly on the individual/direct benefits and risks. Generally, although indirect benefits would not constitute pivotal evidence in the context of regulatory required monitoring, they may also be included as supportive evidence of the benefits of vaccines within vaccination programs. However, in the particular instances where indirect/population-level risks or safety signals are detected and need to be included in the analysis, the perspective would need to be expanded to take into account both direct and indirect risks as well as benefits.


Manufacturers may also need to expand the scope and perspective of benefit-risk monitoring for more internal purposes. The monitoring of both direct and indirect benefits and risks, by providing understanding of the impact/mode of action of their vaccines in real-world programmes that could not have been obtained in clinical trials, is necessary to support both the development of expert knowledge of these vaccines, and their adequate introduction on specifically identified markets.

### 3. Definitions of measures for benefits of vaccination and vaccination programmes

In both areas of assessing benefits (vaccine effectiveness and impact), confusion can arise due to different interpretation of terms. Table 1 provides definitions for main effect measures used in this report.

**Table 1. Definitions for effect measures used in assessments of benefits of vaccines and vaccination programmes**

Effect measure	Definition	Formula / comment*
Vaccine efficacy	The direct effect of a vaccine on the occurrence of the targeted outcome in a individually randomised clinical trial	$VE = (AR_U - AR) / AR_U$
Vaccine effectiveness (VE)	The effect of a vaccine on the targeted outcome in a field study post licensure	$VE = (AR_U - AR_V) / AR_U$ $VE = 1 - OR$ $VE = 1 - RR$
Direct effect	The effect of vaccination on the occurrence of a targeted outcome in individuals who received the vaccine, resulting from immunological protection rather than from reduced transmission in the population. I.e. the decrease in outcome due to vaccination, when the hazard rate of infection is the same	Acts on vaccinated individuals only
Indirect effect / herd protection / herd immunity	The effect of immunisation on the occurrence of a targeted outcome (in vaccinated and unvaccinated individuals) as a result of a reduction in hazard rate of the infection rather	Acts on vaccinated and unvaccinated individuals. Most easily to assess in unvaccinated individuals.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

	than immunological protection.	
Impact of vaccination	Population effect of a vaccination programme or campaign on the burden of disease of the targeted infection	e.g. $VPDI = I_c - I_v = I_c * VE$
Vaccine failure	The occurrence of a specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.	
Primary vaccine failure	Lack of seroconversion or seroprotection in a vaccinated individual due to host or vaccine related factors	
Secondary vaccine failure	Waning of vaccine induced immunity	
Failure to vaccinate	The situation where an indicated vaccine was not administered, or not appropriately administered	
QALY	Quality adjusted life year	[length of time lived with a specific condition] * [value of a health state]
DALY	Disability adjusted life year	length of time lived with a disability * [value of a health state] + years of life lost
Cross-protection	Effect of vaccination on the incidence/prevalence of different serogroups/genotypes of the infection than targeted by the vaccine	
Correlate for protection	A marker of immune function that statistically correlates with protection after vaccination	

\*  $AR_U$ =attack rate unvaccinated;  $AR_V$ =attack rate vaccinated; OR=odds ratio; RR=relative risk; VPDI=vaccine preventable disease incidence;  $I_c$ =incidence in unvaccinated cohort;  $I_v$ =incidence in vaccinated cohort.

## 4. Criteria to assess methods


These below criteria are relevant when assessing methods for vaccine benefit evaluation.

### 4.1 Statistical criteria.

These comprise issues like power to detect an effect; finite sample bias of the effect estimator; and efficiency of the effect estimator. Also included may be issues relating to Type I error probabilities or false discovery rates for multiple testing.

### 4.2 Temporal criteria.

These cover the time to detection or confirmation of an effect, for various specifications of the Type I error probability (or average run length), and also the frequency with which and the

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

speed at which results can be updated. Also perhaps how quickly various study designs can be implemented.

### 4.3 Robustness criteria.

These cover robustness to measured and unmeasured confounding; assumptions required and robustness to model mis-specification; robustness to misclassification of exposure and disease; and dependence on data types.

### 4.4 Operational criteria.

These cover issues such as data requirements, data cleaning or checking requirements, complexity of implementation, and financial cost.

### 4.5 Ethical criteria

These cover issues such as withholding a (moderately) effective vaccine from a population for research purposes only, or choosing when to stop a programme when effectiveness appears low.

## 5. Methods of vaccine benefits assessment pre-implementation of national vaccine recommendations

### 5.1 Randomised controlled trials


Prior to the use of vaccines for routine immunisation, their efficacy is normally established in a series of randomised, double blind, controlled trials. These trials are generally governed by a protocol with an emphasis on measuring the biological efficacy of the vaccine. The general formula for the vaccine efficacy in a trial is:

$$\text{vaccine efficacy} = (AR_u - AR_v) / AR_u = 1 - RR$$

where  $AR_u$  is the attack rate among unvaccinated and  $AR_v$  is the attack rate among vaccinated individuals.  $RR$  is the relative risk of disease among vaccinated compared to unvaccinated individuals.

#### 5.1.1 Individually randomised controlled trial (RCT)

In this design the unit of randomisation for vaccine or placebo allocation is the individual. If randomisation worked well, this results in equal mixing and characteristics of vaccinated and unvaccinated individuals. This allows estimating direct vaccine efficacy. Herd-protection effects are equally present for vaccinated and unvaccinated individuals, and therefore are not included in the efficacy estimate. An example of an individually randomised efficacy trial is the 2011/12 rotavirus vaccine trial in India (2) .

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### 5.1.2 Cluster randomised trials

In this design the unit of randomisation for vaccine or placebo allocation is a cluster of individuals, e.g. a village or a neighbourhood. Vaccine efficacy estimated by using this design is a summary measure of indirect and direct effects of vaccination. It is important in this design that the between cluster transmission of the target pathogen is negligible, that the cluster population is stable over time, and that dependence of outcome events within clusters is taken into account in the sample size calculation and the analyses. Examples of cluster randomised trials are a pneumococcal vaccine trial in American Indian children and a typhoid fever vaccine trial in Pakistan (3),(4).

### 5.2 Stepped wedge designs for vaccine introduction


This design compares vaccinated and unvaccinated groups that arise during a vaccination programme introduction. The design was first used in the Gambia to assess the effectiveness of HBV vaccine (5). Since the unit of vaccine allocation is a cluster, this design can be used to assess indirect effects of vaccination. There are cluster randomised and non-randomised versions of the design, which has been the subject of a systematic review (6).

### 5.3 Burden of disease (BoD) assessments pre-implementation of vaccination programmes

Before a vaccination programme is implemented, BoD assessments are done to quantify the anticipated burden that the programme will prevent. This data is usually required in a decision-making process around introduction of the vaccine. Measures of the impact of an infectious disease in a population should take into account the frequency of occurrence, severity of disease and risk of eventual complications, and mortality. Because prevention measures target diseases that do not inevitably lead to death, but nevertheless can have a debilitating effect on quality of life, a number of summary measures of population health (SMPH) have been proposed to capture the impact of all health-reducing conditions (where ‘condition’ refers to a departure from ideal health, and so includes diseases, disorders, injuries, impairments, and other afflictions). Importantly, these composite measures of population health allow comparison between heterogeneous conditions and their effects on the full spectrum of health (i.e., not just on a single indicator, such as mortality). The most commonly used composite health measures are the quality-adjusted life-years (QALY) and the disability-adjusted life-years (DALY) measures.

In particular, the burden of disease methodology, as for the Global Burden of Disease and Injury Study (GBD), is a suitable approach for capturing the population-level impact of health-reducing conditions, as it allows the relative burden across diseases to be compared, as well as the burden across time for a specific disease (7),(8),(9). However, in the context of vaccine benefits, focus should be on the pathogen, not the health state.

To quantify the impact of both chronic and infectious diseases in terms of quality of life and life expectancy, Murray and colleagues developed a composite measure: the DALY. The idea behind the DALY measure is that the impact of particular disease can be divided into the number of years of life lost (i.e., premature mortality) and the number of years lived with a

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

disease (morbidity) with respect to the ideal life expectancy; the result is a single measurement unit that quantifies the years of healthy life lost attributable to the disease.

Building on the GBD studies and methodology, the Burden of Communicable Disease in Europe (BCoDE) project was initiated by the European Centre for Disease Prevention and Control (ECDC) in 2009 to give insight into the current infectious disease burden within Europe. In this project, methodologies and a software application were developed for estimating the current and future burden of 9 vaccine preventable and 23 other infectious diseases within all EU/EEA member states (10), also using the DALY measure.

The DALY is a member of the family of ‘health gap’ SMPH measures, which aim to quantify the difference between the actual health status and full (ideal) health by making reference to a pre-defined norm (such as a life expectancy of 80 years). A second widely used ‘health expectancy’ measure is the QALY, which also combines mortality and morbidity into a single measurement. Further details on QALYs and DALYs can be found in Annex 1.

### 5.3.1 Vaccine probe studies


This is a specific form of a burden of disease study applying RCT methodology, whereby the reduction in the burden of disease following the use of a vaccine with known effectiveness, can be considered as the burden attributable to the targeted infection (11). The main outcome of the study is the vaccine preventable disease incidence (i.e. vaccine attributable rate reduction). This equals the incidence among controls minus the incidence in the intervention group, which is the same as  $[VE \times \text{incidence among controls}]$ . See also paragraph 6.6.2. The advantage of this method is that it can assess the burden attributable to a certain vaccine preventable disease in settings where pathogen specific surveillance is problematic. An example is the Hib probe study in Lombok, Indonesia, which documented a high incidence of Hib meningitis in that setting (12).

## 6. Methods for vaccine benefit assessment post-implementation of national vaccine recommendations

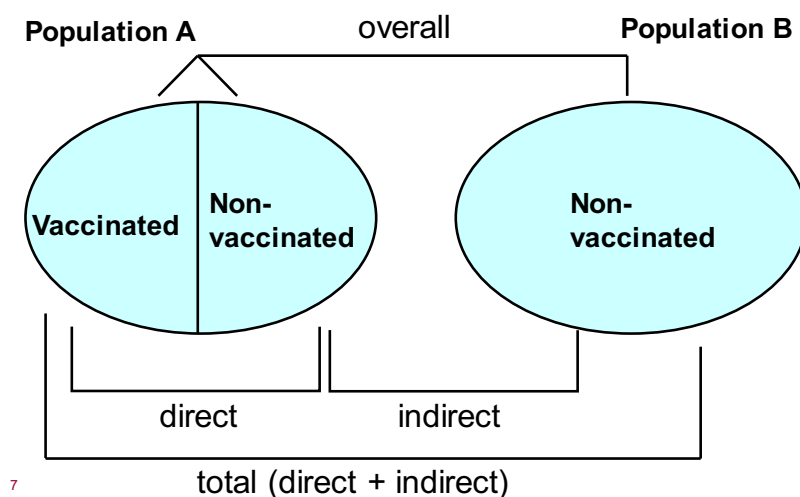
### 6.1 Vaccine effectiveness: Epidemiological methods

Vaccine effectiveness (VE) can be defined as the effect of vaccination on a targeted outcome in a field study post licensure. The outcomes of interest can be infection, carriage, disease, complications and infectiousness. In contrast to vaccine efficacy, VE is the protective effect under ordinary conditions of a public health programme. Here VE can be affected by various factors including inadequate cold chain, faulty vaccine batches, schedule violation, population specific characteristics and changes in the disease epidemiology. Once a programme has been implemented, trials with randomisation and blinding, which would allow estimating efficacy, are usually unethical and impracticable. VE studies are more prone to bias and the interpretation is more complex than efficacy studies.

Effects of vaccination can be differentiated in direct, indirect, total and overall effects (Figure 1.). To assess these different effects, specific study designs have to be used.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

**Fig. 1 Types of effects of vaccination programmes (13).**



### 6.1.1 Cohort studies

In cohort studies, VE can be estimated by comparing attack rates of the outcome among unvaccinated with those in vaccinated individuals, in a cohort of individuals which has had an opportunity to be exposed to the infection of interest and the vaccine. VE is then calculated as:

$$VE=1-AR_v/AR_u=1-RR$$

where  $AR_v$  is the attack rate in vaccinated individuals and  $AR_u$  is the attack rate in unvaccinated individuals.


A typical setting for a cohort study is e.g. a school outbreak (14). Variants of cohort studies are described in chapter 4.2 of the report ‘Appraisal of vaccine safety methods’.

### 6.1.2 Case referent studies

#### Case-control studies

A case-control design to study direct VE is used when cohort studies are not practicable, e.g. when vaccination records are not readily obtainable. Controls are sampled from the same population cases originate from. Group or individual matching can be used to eliminate the influence of known confounders, particularly age. Different approaches to matching in case-control designs (standard matching, counter-matching) are described in the report ‘Appraisal of vaccine safety methods’.

The case-control method enables the estimation of the OR of vaccination among cases and controls, as outlined below:

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO 87/140

	Cases	Controls
Vaccinated	a	b
Unvaccinated	c	d

$$OR = a*d/b*c$$

$$VE = 1 - OR$$

One of the main difficulties in designing case-control studies is to define an appropriate sampling frame for controls. The case-control design has been used to estimate VE for a wide variety of vaccines (15),(16).

### Test negative designs (TND)

This is a case-control design in which controls are patients with a similar disease syndrome who tested negative for the pathogen under study. This approach may rule out differences in (parental) attitude when seeking medical care and of physician differences in making decisions regarding laboratory diagnosis. VE can be underestimated when the sensitivity of the laboratory test is low.

The TND has been used for rotavirus vaccine (17) and influenza (18-20). Considering its intrinsic absence of many biases, the TND is likely to be the best design currently available for observational studies of influenza VE (21).

### Case-coverage designs (screening method)

This method uses data on the vaccination coverage of cases and of the population from which the cases originate. Both coverage estimates are often available from routine surveillance. The screening formula for the VE is:

$$VE = 1 - ((1 - PCV) / PPV) / ((1 - PCV) / PPV) \quad (22)$$

where PCV is the proportion of cases vaccinated and PPV is the proportion of the population vaccinated. Confidence limits for the VE can be obtained by substituting confidence limits for the odds (PCV/(1-PCV)) into the equation above.


Vaccine coverage data must relate to the same population cases originate from, particularly in term of age / birth cohort. Control of confounding by stratified analysis, e.g. by age, is possible.

The screening method has been used to assess VE for a wide variety of vaccines, including mumps, influenza and Hib (23) (24) (1).

The screening method will result in biased VE estimates when cases are clustered in one particular area for which specific vaccine coverage data are not available. The method results in non-robust estimates when values for the PCV or PPV are very high.

### Case-case methods (Broome method, indirect cohort design)

This method can be applied when a vaccine protects against some but not all subtypes of a vaccine preventable disease (VPD), such as pneumococcal disease and human papilloma virus

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

(HPV) (25). The methods considers only cases of the VPD, and compares the vaccine coverage among cases with infections caused by strains the vaccine intends to protect against, with the coverage among cases with non-vaccine serotype infections. An example is outlined in the table below.

	Serogroups included in the vaccine	Non-vaccine serogroups
Vaccinated	a	b
Unvaccinated	c	d

$$OR = [a/c] / [b/d] = a*d/c*b$$

$$VE = 1 - OR$$

The advantage of this method is that it only needs data on cases. An important pre-requisite is that the vaccine should not partially protect against non-vaccine serotypes, ie, that the risk of non-vaccine type disease is the same for vaccinated and non-vaccinated individuals. If there is (some) cross-protection, VE estimates will be underestimated. The method can also lead to biased estimates when the vaccine reduces carriage of strain targeted by the vaccine. In this case, it may be that non-vaccine type carriage is higher in the vaccinated than the unvaccinated due to replacement of carriage. This bias can be quantified by a formula proposed by Andrews et al (26).


Lastly, the Broome method does not take multiple infections in one individual into account, which is relevant e.g. for assessing VE for HPV vaccines. Also relevant here is ‘unmasking’: a higher chance of detecting less dominant types when dominant types are prevented by the vaccine. When this occurs, the Broome method also results in biased estimates.

### 6.1.3 Household studies

Here close networks of a small number of people, such as households or sexual partnerships where an infection is introduced, are studied whereby the index case and all secondary infections among contacts are ascertained. Secondary attack rates (SARs) among vaccinated and unvaccinated contacts are then calculated for each generation of infection whereby excluding past cases and the index case. These SARs are summed for all networks (e.g. households) and generations, and used in the following formula:

$$VE = 1 - SAR_{\text{vaccinated}} / SAR_{\text{unvaccinated}}$$

Studying VE in this way has the advantage that in small, close networks the random mixing assumption is more likely to be met, whereby reducing heterogeneity in exposure among vaccinated and unvaccinated individuals. The latter is a major source of bias in population studies to assess VE.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

This study design requires data on vaccination status and dates of onset of all individuals. A specific bias that can occur arises from a preferential inclusion of networks with a large number of cases. A biased VE estimate can also occur when vaccination affects infectiousness of the disease and when there is heterogeneity in the vaccination coverage of networks. This design has been used for estimating VE for many infections, including e.g. mumps (27) .

#### 6.1.4 Effectiveness against post-infection outcomes (severity and infectiousness)

To assess whether a vaccine affects severity of disease, the study base includes only cases of the infection, among whom a severity marker is compared between vaccinated and unvaccinated individuals. An example of this is VE of mumps vaccine against mumps complications (28). Here it is important that inclusion of severe cases in the study base is independent of their vaccination status.

To assess whether a vaccine affects infectiousness of an individual, it is necessary to study a setting in which it can be ascertained who infected whom and where the contact frequency and intensity is fairly well defined and homogeneous. Households can be used for this, in which the VE is the ratio of SARs among contacts of vaccinated and unvaccinated index cases, respectively (29). Bias can arise when the vaccination status of contacts differs between contacts of vaccinated and unvaccinated index cases – a situation likely to arise.


### 6.2 Vaccine effectiveness: Mathematical models

Before a new mass vaccination programme is implemented, policy makers frequently rely on mathematical transmission models to assess the anticipated benefits of vaccination. Once a vaccination programme has been implemented, observable outcomes can be used to validate the model predictions. Eventual discrepancies between predictions and post-implementation outcomes can be informative of particular aspects of VE that cannot be directly measured in cohort, case-referent or household studies. These aspects are particularly related to the mode of action of the vaccine or the effect of vaccination on infectiousness and transmission. Moreover, transmission models are still useful once post-implementation outcomes are available to provide researchers with counterfactual outcomes once prevention measures have been put in place. These counterfactuals can be employed to assess the overall impact of a vaccination programme, and to extrapolate beyond the observed time period.

#### 6.2.1 Modelling to estimate separate components of vaccine effectiveness

Transmission models explicitly separate exposure to infection from an individual's response to such exposure (infection, illness, complications), and how this response is affected by vaccination. The separation of exposure from response to exposure allows a more precise assessment of the extent of herd immunity that would be hard to quantify without a mathematical transmission model.

Regarding the response to exposure, one may focus on different outcomes, such as infection, infectiousness or illness.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

*Infection as outcome:* for such a specification we need to assign to each individual a probability that exposure would result in an infection, with and without vaccination, where different individuals may have different probabilities.


*Infectiousness as outcome:* we also need to assign to each individual a probability that upon exposure the individual would be infected and become infectious to others, with and without vaccination. Again, different individuals may have different probabilities.

*Illness as outcome:* we also need to assign to each individual a probability that upon exposure the individual would become ill, with and without vaccination, where different individuals may have different probabilities.

Multiple probability distributions for each outcome may result in the same frequency of observed events. For instance, if 10% of vaccinated individuals become ill upon exposure, this might be indicative of a 0.1 probability to be infected or of a 0.1 probability to become ill given infection. In both cases, VE against illness would be the same but we are clearly talking about different effects with relevance to transmission of the infectious agent. In addition, one has to consider the individual heterogeneity in the response to exposure, with or without vaccination. For instance, when all vaccinated individuals have exactly the same probability of say 0.6 that exposure leads to infection, we refer to the mode of action of the vaccine as “leaky”. When the individual probabilities that exposure of a vaccinated individual leads to infection are either 0 or 1 with a proportion of say 0.4 and 0.6 in the population, we refer to the mode of action of the vaccine as “all or nothing”. In both cases the VE against infection is the same but again the impact of vaccination can be quite different, both for the vaccinee and for the population as a whole.

Epidemiological VE studies are not generally aimed at distinguishing whether a reduction in the incidence among those vaccinated is due to a reduced probability of exposure to infection, of infection given exposure and/or of illness given infection. Neither are they usually designed to assess the mode of action of the vaccine. To distinguish between various aspects of VE, and to highlight uncertainty with regard to the long-term impact of a vaccination programme, mathematical transmission models can be used that can integrate all available information on the level of the individual and the population, provided data is available.

The recent large-scale introduction of rotavirus vaccination in the USA provides a good example of the merit of mathematical modelling to assess VE (30). Prior to vaccination, annual rotavirus epidemics showed a clear spatiotemporal trend. A transmission model calibrated against spatiotemporal data showed that differential timing of rotavirus epidemics could be described by variation in birth rates. This finding has relevance to the post-implementation pattern of rotavirus activity because vaccination effectively reduces the recruitment of susceptible individuals, akin to a decline in birth rate. The validated model (on pre-implementation data) could be used to explore the relative importance of direct and indirect protection provided by rotavirus vaccination, and to assess the relative VE of one-dose vaccination compared with the full protective VE conferred by three-dose vaccination,

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


which was estimated at 70%. This is an example of the added value of mathematical modelling in assessing VE next to epidemiological study designs, especially when epidemics display complex spatiotemporal dynamics.

### 6.2.2 Models to study changes in vaccine effectiveness over time

Changes in VE over time due to boosting and waning immunity can be assessed by consecutive serological surveys. The analysis of serological surveys is greatly facilitated through the use of transmission models, as these allow for the specification of a time-varying age-specific force of infection. As a result, transmission models can distinguish between immune individuals who have been infected a long time ago and have never been exposed to infection since, and immune individuals who have been infected a long time ago and have been exposed to infection since. For the first group we expect that immunity “waned” and individuals might become susceptible to reinfection, for the second group we expect that immunity is “boosted” and individuals are not susceptible to re-infection (or at least disease). The epidemic SEIR model is useful to study the impact of vaccination on infection dynamics. For most infectious diseases, however, we have to add more compartments to do justice to the complexity of the infection cycle and the time course of immunity. Transmission models might become particularly complex if pathogen diversity or pathogen adaptation has to be taken into account. Changes in VE over time might be indicative of changes in the composition of the pathogen population over time, either driven by exogenous factors or in response to selective pressure exerted by mass vaccination. The recent resurgence of pertussis observed worldwide has been attributed to the switch from whole-cell vaccines to less effective acellular vaccines, waning immunity and pathogen adaptation (36). However, the changing epidemiology of pertussis in the vaccine era could also be reproduced by an age-structured model that accounted for changes in age-specific contact patterns as determined in a detailed contact network study (37). While this modelling study deliberately ignored the other possibilities that have been proposed as explanations for the resurgence in pertussis incidence and mortality, it goes to show that contact structure is a pivotal element for understanding age-specific incidence rates, and ignorance of changes in transmission dynamics is likely to result in misinterpretation of epidemiological data.

### 6.3 Indirect vaccine effects

Indirect effects of vaccination can be defined as the effect of vaccination on the occurrence of a targeted outcome (in vaccinated and unvaccinated individuals) as a result of a reduction in hazard rate of the infection rather than immunological protection. Indirect effects can be most readily estimated by comparing the occurrence of the outcome of interest in unvaccinated individuals in a population in which the vaccine programme was implemented, with the occurrence in unvaccinated individuals in a population in which the programme was not implemented (Fig. 1). A cluster designed trial, or a stepped wedge implementation of a vaccination programme allow estimating indirect effects (see above). Post-implementation, indirect effects can be observed by comparing the occurrence of disease in a non-vaccinated population with historic data from before implementation of the vaccination programme. A vaccine can cause indirect effects by e.g. reducing the incidence, infectiousness or prevalence

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

of carriage of a pathogen in vaccinated individuals. Large indirect effects have e.g. been observed for pneumococcal vaccination programmes, where the incidence in untargeted elderly decreased due to vaccination of infants (38) .

## 6.4 Vaccine failure

Vaccine failure is the occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization<sup>1</sup>. This definition is generic and requires specific adaptation for each disease/vaccine, considering the following criteria: intended immunization goal, specificity of clinical symptoms/diagnosis, kinetics of protective immunity and the natural history of disease (39). This requires clinical and laboratory confirmation (or an epidemiological link to a confirmed case, where applicable) that the actual disease is vaccine preventable, i.e. that the pathogen (including, where appropriate, type, subtype, variant, etc.) and clinical manifestations are specifically targeted by the vaccine. In case of a live attenuated vaccine such as measles, it is possible to distinguish disease caused by the vaccine from wild-type infection by subtyping the virus. There are no internationally agreed definitions for vaccine failure of specific vaccines.

Monitoring vaccine failures is done by public health agencies as part of monitoring effectiveness and impact of vaccination programmes. Vaccine manufacturers monitor vaccine failures as part of pharmacovigilance. To assess VE and impact, the rate at which vaccine failures occur in a population has to be considered alongside information on coverage. At constant VE, an increase in coverage will result in increasing impact but also an increasing rate of the occurrence of vaccine failures.

## 6.5 Interpretation of vaccine efficacy and effectiveness estimates


### 6.5.1 Causality: efficacy and effectiveness

The causal effect of an intervention on the outcome of interest can only be assessed by a trial where subjects are randomized into different treatment regimes. For vaccines against infectious diseases, clinical trials are more complicated than e.g. a therapeutic drug trial because we have two exposures: exposure to vaccine and exposure to infection. Usually (except in challenge studies) we assign exposure to vaccine at random, but cannot assign exposure to infection as that would usually be unethical. Hence, exposure to infection can be a confounder even in randomized controlled vaccine trials (40). It follows that we cannot infer the causal effect of a vaccine from observational studies. We refer to vaccine efficacy and effectiveness to distinguish between the effect of a vaccine that is likely to be causal and the effect that might, but need not be causal.

### 6.5.2 Mode of protection: All-or-nothing versus leaky

From the model of vaccination effects it is clear that we have to distinguish between ‘leaky’ and ‘all or nothing’ modes of vaccine action (see paragraph 6.2.1). If we could conduct trials

<sup>1</sup> Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012. Available from: [http://whqlibdoc.who.int/publications/2012/9789290360834\\_eng.pdf](http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf)

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

where individuals were assigned to exposure to infection (usually considered unethical), we could easily observe which mode applies: if individuals exposed once have a higher vaccine efficacy than individuals exposed several times we have a leaky vaccine; if individuals exposed once have the same vaccine efficacy as individuals exposed several times we have an all or nothing vaccine.

From observational (ecological) studies we could deduce which mode of action applies if we can compare individuals with different degrees of exposure to infection, and if we could correct for differences in exposure. As exposure to infection cannot be measured precisely, we can explore the mode of action of a vaccine in an epidemic model if we had good information about the contact network structure.

### 6.5.3 Effectiveness against infection, carriage, illness, severe illness, death, infectivity

The outcome of interest of a VE study may differ: it could be infection, carriage, illness, severe illness, death, infectivity. The VE against infection can differ from the VE against illness. It would require large and unethical trials to distinguish all the VEs of interest. However, we can explore the differences between these VEs in a mathematical model.

### 6.5.4 Direct and indirect effects


Vaccination lowers the incidence of infection, hence all individuals in the population (vaccinated and unvaccinated) will have a lower probability of being infected per unit of time. Thus, unvaccinated individuals (and vaccinated individuals with vaccine failure) benefit from others being vaccinated by having a higher probability of escaping infection. Such effects are usually referred to as herd immunity. Herd protection may be a more appropriate term since there is no immunological mechanism behind this effect.

The direct effect of vaccination is the decrease in outcome due to vaccination, when the hazard rate of infection is the same. The indirect effect of vaccination is the decrease in outcome due to decrease in hazard rate of infection. Direct effects are measured in individual-level clinical trials. Indirect effects are captured in cluster-randomized trials. Precise estimation of the causal indirect effect of vaccination requires carefully designed household studies (41).

## 6.6 Impact of vaccination: Epidemiological methods

### 6.6.1 Impact on disease occurrence

Impact of a vaccination programme is a summary measure that includes factors such as coverage achieved, overall VE and effects of behaviour changes. In this respect, impact is usually of more importance to guide public health decisions than VE per se. Impact can be considered specifically for the infections targeted by the vaccine, for all diseases caused by a certain pathogen, or for clinical syndromes such as pneumonia. The less specific the outcome is that is being considered, the lower the impact of vaccination generally is. Less specific outcomes take into account which part of the disease burden is caused by the targeted pathogen, and are hence population specific.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	94/140

When a vaccine is effective against one specific strain of an infection, and when removal of this strain leads to an increase of another strain against which the vaccine is not effective, we can see that the VE against the vaccine-specific strains is positive, but VE against disease is modified by the extent of type replacement. The overall impact of vaccination might even be negative, if the replacing strain displays an increased virulence once vaccine-specific strains have been eliminated.


Impact of vaccination programmes is typically assessed by ecological designs, comparing the occurrence of disease before and after implementation of the programme, or between areas where the programme has and has not been implemented (42). This approach is limited by lack of access to historic data, changes in case definition over time and inability to project trends in incidence in the absence of vaccination. Regardless of these limitations, much insight could be gained by analyses of VPD time-series data from different European countries with different levels of uptake.

### 6.6.2 Impact on the burden of disease

A standard approach to assessing the health impact of a public health intervention is in terms of QALYs gained or DALYs averted (or saved) attributed solely to the intervention. This approach necessarily requires the assumption that there is a causal effect of the intervention on averted burden. In the case of vaccination programmes, both infection and transmission are prevented by effective vaccines, and therefore they can have both direct and indirect effects on disease burden.

Estimation of the disease burden prevented by vaccination strategies, as measured by QALYs gained/DALYs averted, is one suitable method for evaluating retrospective or prospective vaccine deployment (43). One example of a study of quantifying the benefits of vaccination on disease burden in the developed world is a recent retrospective analysis of the relationship between national-level vaccination coverage for measles and measles disease burden within EU/EEA countries in the period 2006–2011 (44). Results indicated an overall reduction of 0.98 DALYs per 100,000 persons for every percentage point increase in coverage. Quantitative measures of burden such as the DALY need to be interpreted through comparison either over time, between populations, or across diseases.

Vaccine preventable disease incidence (VPDI) has recently been proposed as an alternative to VE as a measure of intervention effectiveness (45). This takes into account the background disease incidence and is therefore especially useful in settings where VE is relatively low. The VPDI is calculated from e.g. a clinical trial simply as the incidence in the control group minus the incidence in the vaccinated group. An analogue can be imagined, vaccine preventable disease burden, which could be quantified simply as the DALYs associated with the occurrence of a particular disease in the unvaccinated segment of the population, minus the DALYs calculated for the same disease in vaccinated individuals in the same population. Such a measure could be computed retrospectively or prospectively. Two variants of the DALY measure, DALYs/100,000 population and DALYs/case, would be applicable to the estimation of prevented burden when comparing unequal population sizes and when comparing vaccine-preventable diseases that differ in severity, respectively.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

When the DALY methodology is applied to assess the impact of vaccination strategies on disease burden, it is most practical to adopt the pathogen-based approach, as attribution of the incidence or prevalence of a given health state among the set of possible pathogens that could have caused it is therefore not required.

## 6.7 Impact of vaccination: Mathematical models


### 6.7.1 Modelling dynamic effects when there is no endemic equilibrium

Upon introduction of mass vaccination, we frequently see a “honeymoon period”, where the overall level of protection in the population is high because of pre-existing natural immunity among non-vaccinated individuals in combination with vaccine-induced immunity among otherwise susceptible individuals. During this honeymoon period the incidence of the disease can be very low, the infection might even disappear from the population. When the infection disappears from the population, new recruits to the at-risk population who are not vaccinated remain susceptible and a pool of susceptibles will accumulate, facilitating reintroduction with recurrent outbreaks of the infection (31).

Epidemic cycles can be captured by mathematical transmission models, such as the SEIR model: individuals are either susceptible, exposed to infection but not infectious, infected and infectious, recovered and immune. These models can reproduce the honeymoon period after introduction of vaccination, followed by recurrent epidemic waves (32). When estimating VE from observations, it is important to carefully select study populations and the time period over which incidence or prevalence measures will be compared. When incidence and prevalence for infectious diseases are highly dynamic, epidemic models can be used to simulate how the dynamics of incidence and prevalence would affect the estimated VE.

An important topic in vaccination programmes is the possibility of eliminating disease, e.g. measles, from a population (33),(34). Elimination requires maintaining the effective reproduction number  $R < 1$ , by achieving and maintaining low levels of susceptibility in the population. Designing an elimination programme for a particular population involves setting target levels of susceptibility, establishing the current susceptibility profile, selecting an approach to reduce susceptibility below the target and to maintain susceptibility below the target. Mathematical transmission models play a role in each stage of the design of elimination strategies.

A key indicator of the sustainability of an elimination programme is the residual level of susceptibility of a cohort after it has completed its scheduled vaccination opportunities. This can be estimated from vaccination coverage data. Surveillance of cases can also be used to monitor the effective reproduction number  $R$ . After the elimination of endemic transmission from a population, all cases are linked to infections imported from outside the population. The expected distribution of the size of outbreaks depends on  $R$ ; the larger the value of  $R$ , the larger and longer the outbreaks. Monitoring the proportion of imported cases and the size and duration of outbreaks enables  $R$  to be estimated (35). This in turn provides information about the effectiveness of vaccination in reducing transmission throughout the population.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### 6.7.2 Extrapolating from intermediate outcomes to disease endpoints


In some instances, VE against disease cannot be established in a clinical trial because of ethical or logistic reasons. An example is vaccination against human papillomavirus (HPV), an infection which can induce various forms of cancer. In vaccine trials and observational cohorts, VE can only be assessed against infection or against cancer precursors since waiting for the occurrence of cancer would be unethical and would take too long. In such instances, mathematical models can be employed to provide an estimate of VE against illness, e.g. cervical cancer in the case of HPV.

VE against infection levels or disease precursors can be different from VE against illness. Whether VE against infection or disease precursors is larger or smaller than against “downstream” outcomes, such as cancer, depends on the specificity of a particular cause. For instance, it is assumed that HPV is causally related to all cases of cervical cancer, and that about 70% of cases are caused by vaccine types. Non-vaccine types however contribute to a substantial higher proportion of pre-malignant lesions. Because of this, VE against cancer precursors is less than 70%. On the basis of a dynamic model for multiple oncogenic HPV types, the current HPV vaccination programme has been estimated to effect a 68% reduction in cervical cancer incidence at a 90% female vaccine coverage, whereas the detection rate of pre-malignant lesions is expected to reduce by only 44% (46).

In general, estimates of VE will be overly optimistic if a particular outcome (such as illness) can be caused by pathogens that are not prevented by the vaccine, unless one accounts for the other causes in analyses. Importantly, cause-specific rates may change as a result of vaccination, because causes other than those removed by vaccination may become more apparent post-implementation. Epidemiological studies could be designed to account for such effects, but the design and interpretation of outcomes likely requires pivotal input from mathematical models.

### 6.7.3 Modelling herd-protection

Herd protection denotes the effect of vaccination on reduced transmission throughout the population. Herd-protection is difficult to assess in observational studies, but may be inferred by the use of transmission models. Clearly, herd-protection effects are beneficial to the impact of vaccination on the burden of disease if vaccination results in a reduced exposure to infection. As the proportion of the population that is vaccinated increases, the incidence of infection will decrease. However, for those who are not vaccinated and susceptible, it takes a longer time before they encounter someone who is infectious. Their age at infection will be higher than the average age of infection before vaccination was introduced. If the probability of complications upon infection increases with age, the risk of developing complications upon infection will be higher for those who are not vaccinated, and for those with vaccine failure. At the population level, the increased protection of those who received the vaccine does not necessarily outweigh the increased burden of disease due the shift in the age of infection. An infamous example is rubella, where the shift in the force of infection to older age groups can have dangerous implications. Immunization of infants led to an increased infection hazard among women of child-bearing age, with an increased risk of congenital rubella syndrome

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	97/140

(CRS) as an adverse outcome of vaccination. In Greece, a country where vaccination coverage for rubella remained consistently below 50% after vaccine introduction, the occurrence of CRS increased after the introduction of mass immunization (47).


#### 6.7.4 Modelling long-term dynamic effects (beyond the ‘honeymoon-period’)

After introduction of vaccination against childhood infections, on the timescale of about one human generation (30 years) we might see an additional shift in epidemic dynamics because infants now acquire their maternal antibodies from mothers who are vaccinated rather than from mothers who were naturally infected. After introduction of vaccination against a few selected strains of a multistrain pathogen, such as pneumococcus, the composition of circulating pathogen strains might change. We expect fewer strains that are targeted by the vaccine, which might result in increased incidence of disease caused by strains that are not targeted by the vaccine. This effect is referred to as type replacement, and can denote an increased transmission as well as an increased virulence of non-vaccine types. Consequently, a vaccine that protected against the most dominant circulating strains in the first years after introduction might protect against only a few of the circulating strains in the long term, and the net effectiveness of a vaccination programme will decline as a result.

Modelling long-term dynamic effects of vaccination requires a thorough understanding of the transmission dynamics of vaccine-preventable pathogen strains and possible ecological interactions with non-vaccine strains or even with other pathogens. The increased prevalence of non-vaccine types in invasive pneumococcal disease has been attributed to weak serotype-specific immunity and a non-specific acquired immune response, permitting a high diversity of pneumococcal serotypes and a complex response to vaccination against specific serotypes (48). Likewise the occurrence of other pathogens, such as *Staphylococcus aureus*, is also modified by pneumococcal vaccination, a finding that is indicative of the dynamic interplay between viruses and bacteria in the microbiome of the upper respiratory tract (49). Clearly, only models that incorporate much prior information as well as expert knowledge of the biological system at hand can predict such long-term effects of vaccination. Conversely, observed outcomes of vaccination programmes can be used to inform such models and to project the impact of vaccination further into the future. This knowledge can also be used to assess the effectiveness of changes to a vaccination programme, e.g. the substitution of one polyvalent vaccine by another as recently happened with regard to pneumococcal vaccine.

#### 6.8 Immunogenicity and correlates for protection

A correlate for protection is defined as ‘a marker of immune function that statistically correlates with protection after vaccination’ (50). This immunological marker can be a serum antibody level, mucosal antibodies or a cellular immunological characteristic (e.g. Th17 activity). Of these, only assays for serum antibody levels are standardised to a certain extent. Identification of correlates for protection for a specific infection is a crucial step in vaccine development. Furthermore, they allow the assessment of individual and population immunity. For many vaccines, efficacy trials are not feasible due to large sample sizes required (e.g. for meningococcal B disease (51)). Trials of a new vaccine can also be deemed unethical when an

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

effective vaccine for a certain indication has already been licensed. In those instances, data on correlates of protection can be used to bridge from or supersede efficacy trial data.

Methods to identify correlates of protection include studies into levels of passively acquired or maternal antibody that protect, analyses of immune responses in protected and susceptible individuals in efficacy trials, very early (or pre-exposure) sampling of vaccine failures, human challenge studies, extrapolation from animal challenge studies or using VE estimates. The latter method was described by Siber et al and was recently used for pneumococcal disease (52).

## 6.9 Sero-epidemiology

For diseases for which a (reasonable) serological correlate for protection exists, population benefit from vaccination can be quantified by a serological survey assessing which proportion of the population has antibodies above the cut-off for protection. Serum samples can be obtained from a dedicated population survey (53) or from residual samples from e.g. diagnostic testing (54). In addition to assessing immunity, sero-epidemiology can also be used to evaluate the prevalence and incidence of infection.

## 7. Evaluation of the available methods


The assessment of strengths, weaknesses and gaps in available methods for assessment of vaccine benefits was undertaken in two ways. Firstly, two real-life scenarios of where the assessment of VE led to a decision regarding the use of the vaccine were shared with selected ADVANCE stakeholders for commenting (Annex 2). The comments of stakeholders are included below. A second assessment of methods was done in a meeting with stakeholders, some of whom attended by telephone (dd 7/7/2014). General criteria to assess methods (paragraph 4) were kept in mind during the assessment. Results are summarized below.

In general, benefit evaluations usually require multiple datasets of possibly various sources with methods of varying robustness, and comparisons are sometimes made outside of statistical validity.

### 7.1 Effectiveness methods

Some limitations apply to most methods of assessing VE. A key limitation is the amount of time needed generally to assess VE. Real-time monitoring of VE is important for optimal use (and disuse) of vaccines (albeit less so than real-time monitoring of risks) but it is rarely done. Delays are often linked to absence of relevant data, e.g. when routine surveillance does not capture the relevant information in sufficient quality or when reconciling data sources is complicated. Delayed availability of laboratory confirmation of suspected cases is contributing to these delays. Methods that can deal with data inadequacy are lacking. Influenza is an example where VE assessments are carried out relatively fast (55),(18). The essence of methods employed here is that they are based on an enhancement of routine surveillance, whereby data is collected not only for cases but also for test-negative cases.

A difficulty with VE estimates from an ethical perspective is when to consider a VE too low to justify use of the vaccine in a public programme: Is it ethical to withhold a moderately

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

effective vaccine? This decision needs to balance the risks of the vaccine and of the programme against the risk of the disease and complications.

### 7.1.1. Pre-implementation of a national vaccine recommendation

Randomised controlled trials (RCTs) are the gold standard method since they avoid important biases that result when vaccine allocation is associated with the outcome. The main limitation of RCTs is that they are very expensive, can take much time to complete, can be deemed unethical, and can be impracticable due to a low incidence of disease or in populations already vaccinated against the disease of interest. Individually randomised trials can only be used to study direct vaccine effects. Ethical approval is always needed and obtaining this can be more complex than for observational studies. These limitations, except for the financial one, can also apply for stepped-wedge designs. In addition, stepped-wedge designs usually cannot blind vaccine allocation and those assessing disease outcomes, which can lead to a biased VE estimate (ref Brown 2006).

A more general limitation of trials is that it is uncertain how results will translate to real-life, where vaccines e.g. prophylactic use of paracetamol or co-administration of other vaccines can reduce effectiveness (56).

### 7.1.2. Post-implementation of a national vaccine recommendation


#### 7.1.2.1 Epidemiological methods

Epidemiological methods used for VE assessment post-implementation include cohort, case referent, and household designs (paragraph 6.1).

#### *Classification of outcomes*

All of the epidemiological methods suffer from bias when there is low sensitivity and specificity of the diagnosis or case-definition of the outcome. Lack of sensitivity can be non-differential (when affecting vaccinated and unvaccinated groups equally). In this case, the power of the study will be reduced, but the VE estimate will be unbiased. However, differential sensitivity, e.g. when diagnosis of infection is more difficult in vaccinated cases, can result in important under-estimation of the VE. Low specificity of diagnosis or case definition biases VE estimates also towards zero. The specificity of clinical diagnoses generally drops when a disease becomes less common, which is typically the case when diseases are controlled by vaccination (57). Some designs (Broome methods, test-negative case control method) are less affected by these biases since they are case based. An exception of this is a low sensitivity of a diagnostic test, which will bias VE estimates derived by test-negative case control studies towards the null (except when the sensitivity differs between vaccinated and unvaccinated cases). A low specificity will normally underestimate VE (except when differential). For influenza e.g., there is now consensus that very specific end-points (i.e. PCR confirmed influenza) are needed. Using influenza serology to confirm cases nearly always overestimates VE, as among vaccinated individuals (in contrast to unvaccinated ones) there is no serologic evidence in >75% of PCR confirmed influenza infections (58).

#### *Vaccine exposure*

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

An important limitation of observational studies is that the exposure to vaccination in many cases is not independent from the risk of exposure to the infection. This can over-estimate VE when there is the ‘healthy vaccinee effect’ (59) or underestimate VE when there is ‘confounding by indication’ (60). Methods to adjust for these biases are mainly dependent on the quality of data on health status (or frailty) that is available. Hottes et al. showed high rates of hospitalization and death among those forgoing vaccination after having twice consecutively received the vaccine in the past, indicating that alteration of vaccine behaviour is a robust predictor of death (59). However, the opposite could also be true, i.e. seeking vaccine after forgoing several years because of change in health / risk status. Immunized and non-immunized individuals are not comparable and adjustment for standard confounders can exacerbate the difference.

Misclassification of exposure to the vaccine will also lead to biased estimates.

Unequal risk of exposure to the pathogen, e.g. due to heterogeneity in mixing between vaccinated and unvaccinated populations, can lead to greatly over-estimated VE. Data and methods to account for this heterogeneity are mostly lacking. However, if data on relevant co-variables (e.g. region or socio-economic status) is collected, adjustment for this to some extent may be possible.

#### *Past exposure to the infection*

An important limitation of using observational epidemiological studies is that it is problematic to assess VE in populations where there has been substantial exposure to the pathogen in the past. This can lead to underestimating the VE when this exposure was more common in unvaccinated populations. Natural infection may have also boosted vaccine protection, giving higher VE values. Serological surveys and historic surveillance data are important here to assess the prevalence of past –infection in study populations.


#### *Extreme coverage, VE or incidence*

VE will be underestimated by epidemiological studies when they are based in outbreaks. This is because larger outbreaks occur differentially in pockets of primary vaccine failures, and the larger outbreaks tend to be those which are investigated (61) .

Assessing VE in populations with very high or low vaccine coverage, or when the VE is very high, is problematic since there are too few vaccinated or unvaccinated individuals, or individuals with the disease, respectively.

#### **7.1.2.2 Mathematical modelling**

The key difference between VE estimates derived from epidemiological studies and those derived from mathematical modelling, is that the former is defined by the method of estimating the VE (e.g. screening method), whilst the latter is defined by the actual effect of vaccination on the risk of infection (e.g. VE is the reduced chance of infection conditional on a single exposure in a vaccinated individual). By making specific assumptions, one can equate the one with the other. In mathematical models, these assumptions are usually made explicit, whilst in epidemiological studies they are usually implicit. This use of the same term for different entities complicates comparison of results and the interpretation.

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

A limitation of mathematical models is the relative scarcity of the number of professionals with specialist skills needed to implement the models and to interpret these (particularly when transmission dynamic models are used).


## 7.2 Impact methods

These include mainly ecological methods, comparing the occurrence of disease in populations who are exposed to the vaccine and those who are not. The main underlying assumption here is that the populations are the same in any factor other than the vaccination coverage and the occurrence of the outcome; and that there is no transmission of the pathogen between populations (62). When a before/after design is used, changes over time in disease classification and underlying trends can lead to biased estimates of impact of the programme. To provide more robust estimates of impact, understanding determinants of secular trends is necessary in order to adjust for these. This is not limited to the infection targeted: an understanding of trends in other factors that influence the occurrence of the targeted disease is important (e.g. the occurrence of influenza when considering impact of pneumococcal vaccination). Conversely, reducing the incidence of the target disease can also result in an opportunity for competing pathogens to increase. These can be other serogroups in pneumococcal disease, but also different bacteria (e.g. staphylococcus). These changes may be important for the overall burden of disease. However, current understanding of interaction of pathogens in mucosa (‘microbiome’) is too limited to decide which pathogens to consider.

## 7.3 Burden of disease methods

Currently employed approaches to burden estimation of VPDs have several limitations. Firstly, they usually do not include the burden of disease related to adverse events following vaccination. Second, they cannot attribute burden appropriately in the case of disease caused by multiple pathogens (e.g., bacterial pneumonia occurring after influenza). Third, they do not account for the dynamic nature of the affected population, such as demographic change (eg. the ageing of the population and increasing trends in life expectancy), and the role of infection transmission dynamics (by coupling the predictions of a transmission model). Furthermore, along with the choice of different life expectancy values for males and females (which reflect biological and lifestyle differences), which implicitly value female life-years more than males, the derivation of the severity weights required by both measures has been criticised. Ideally such weights -- normally based on expert panels in the case of the DALY approach -- would be independent of country- or cultural-specific variation in the perception of disease severity, but achieving this in practice is extremely challenging.

Both SMPH measures have advantages and drawbacks. Utility weights required by the QALY measure are virtually non-existent for young children, and methods for obtaining them are subjects of debate (63). If the DALY measure is calculated using residual life expectancy at time of death (the usual method), then there are situations in which a life-extending intervention can paradoxically increase the disease burden, compared with no intervention (64). However, this primarily occurs among older patients who are given a treatment that extends life for a limited time, which is lived under a high degree of disability. The practical

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

solution is to use a reference life expectancy for both intervention and no-intervention scenarios.

#### 7.4 Immunogenicity and sero-epidemiology

These methods are widely used to license vaccines, make decisions on their use, and to evaluate the effectiveness of vaccination programmes. Usually serological results are used (either EIA or functional assays), since there are few defined assays for cellular or mucosal immunity, and if available these assays are extremely labour intensive. Hence, the information available reflects only antibody mediated immunity, which gives a very incomplete picture. The relevance of this limitation differs by pathogen.

The main limitation of serological methods to assess immunogenicity and the proportion of the population that is protected, is that correlates of protection are often unknown or uncertain (50). This is more so with EIA measured antibodies than with functional assays. Especially in case of a multi-antigen vaccine such as pertussis, correlates of protection may be difficult to identify. For both types of assays, it is usually uncertain how immunogenicity translates to VE against infection or against chronic infection. A recent study from the UK e.g. demonstrated that the assumed correlate for protection for 10- and 13-valent pneumococcal vaccine (0.35 ug/mL) used for licensing these products, was probably too low, and that serotype specific correlates vary widely (52). For many diseases correlates of protection are completely lacking (e.g. pertussis), whilst for other they are based on very small studies (e.g. the measles correlate is based on 8 children with measles). Lastly, even when a robust correlate of protection is known, it is uncertain how this relates to long-term protection.

Another limitation of immunogenicity studies and sero-epidemiology is that these studies usually are relatively expensive and take more time to complete than retrospective epidemiological studies where data is available. E.g. a study with vaccine administration at 2, 4 and 6 months of age is expected to generate results in 2-3 years after initiation. However, this can compare favourably to trials where accumulation of a sufficient number of individuals with a clinical endpoint needs to be awaited.

In immunogenicity studies, insight in batch-to-batch variability of vaccines and sensitivity/specificity of serological tests is necessary to be able to assess implications of results.


Lastly, for pathogens where the vaccine protects against only part of existing serotypes (e.g. pneumococcal disease, HPV), the distribution of strains in the population is needed to predict strain coverage of the vaccine. Historical data on this can be scarce, and the validity of methods to identify serotypes needs to be confirmed.

### 8. Experience from other projects and systems

In this section we have listed projects which have relevant output regarding methods for vaccine benefits assessment.

#### 8.1 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) was established in 2006 by the European Medicines Agency (EMA) in

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	103/140

collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. Its goal is to further strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies focusing on safety and on benefit:risk, using available expertise and research experience across Europe. One of ENCePP's products is a guide on methodological standards in pharmacoepidemiology, with a chapter on vaccine safety and effectiveness <sup>2</sup>.

## 8.2 I-MOVE

I-MOVE is a European network which aims to assess the effectiveness of influenza vaccines (65). I-MOVE serves as a platform to exchange views on methods to estimate influenza VE. Expertise of I-MOVE was used to generate guidance for protocols to assess influenza vaccine effectiveness <sup>3</sup>.

## 9. Conclusions and recommendations

In this report we made an inventory of methods to assess benefits of vaccination and of vaccination programmes. Benefits in this context were defined as VE and impact. Both measures are highly relevant for all stakeholders in the field of vaccination (the public, public health authorities, academia, vaccine manufacturers and regulating authorities).

The central underlying issue that complicates assessing vaccine benefits on a population and individual level is that of the counterfactual: an ideal assessment of effectiveness and impact of vaccination would involve observing what would have happened if an individual or population would have not been vaccinated given all other factors remained unchanged. Limitations in making inference on the counterfactual leads to biased and imprecise estimates of benefits.


From the assessment of strengths, weaknesses and gaps of methods identified we conclude that it is impossible to select one method as the best: the appropriateness of methods depends on the data available, the possibility to use the methods (in terms of e.g. budget or ethical limitations), the demands that are put on the results (in terms of e.g. robustness, validity and timeliness) and the perspective of the decision maker (e.g. manufacturers, public health or regulators). Specifying requirements of methods by understanding and thinking through the policy decisions ahead and their implications is key to select the appropriate method. The diversity in programmes and coverage of programmes in Europe could be used more to assess impact and effectiveness.

An important finding arising from the review of methods is the variety in different interpretations that are given to the terms VE and impact of vaccination. Some define VE and impact by the method of estimation, whilst other use a mechanistic definition. The scope of the term impact is also open to multiple interpretations: e.g. the impact on the occurrence of the targeted pathogen or on the burden of disease of a certain condition. Our recommendation

<sup>2</sup> [http://www.encepp.eu/standards\\_and\\_guidances/methodologicalGuide9\\_2.shtml](http://www.encepp.eu/standards_and_guidances/methodologicalGuide9_2.shtml)

<sup>3</sup>

[http://ecdc.europa.eu/en/publications/publications/0907\\_ted\\_influenza\\_ah1n1\\_measuring\\_influenza\\_vaccine\\_effectiveness\\_protocol\\_case\\_control\\_studies.pdf](http://ecdc.europa.eu/en/publications/publications/0907_ted_influenza_ah1n1_measuring_influenza_vaccine_effectiveness_protocol_case_control_studies.pdf)

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


here is to be as specific as possible when reporting benefits of vaccination and of vaccination programmes, and to make methods and assumptions underlying inference and interpretation, and to whom these apply (individuals or population), explicit.

One observation that stood out is that often the process of assessing benefits is of insufficient timeliness to guide policy making when dedicated data collection is needed. Routinely available data is often incomplete and of insufficient quality to use. This could be overcome by making small adaptations to routine data collection (e.g. to also collect vaccination status of non-vaccine strain pneumococcal disease cases so that the Broome-method can be employed) and by developing methods that can adjust for low quality of data (e.g. low sensitivity of diagnostic tests).


Lastly, we conclude that there is a lack of methods that can be employed to assess VE in situations where there is very high or low coverage of the vaccine. In these situations, the lack of (un)vaccinated individuals precludes the types of epidemiological studies listed here. Using a priori knowledge in a Bayesian framework may bring assessments in this context further (e.g. concluding measles VE is high when very few cases are observed in a population with high coverage that is occasionally exposed to measles). It can be argued that in the situation with high coverage and few cases, monitoring VE is less of a priority than e.g. monitoring the effective reproductive number ( $R_e$ ).

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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	106/140

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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	108/140

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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

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	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## ANNEXES

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	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## Annex I VACCINE COVERAGE

Table A1. Diphtheria articles retained from the literature search.

Country	No. of abstracts	Surveys		Register data	
		National	Sub-population	National	sub-population
France	16	3	13		
Germany	7	3	4		
Switzerland	5	1	4		
Greece	5		5		
Italy	3		3		
Belgium	2		2		
The Netherlands	3			1	2
Spain	2		2		
United Kingdom	1		1		
Denmark	1			1	
Slovenia	1				1
Serbia	1				1

Table A2. Pertussis articles retained from the literature search

Country	No. of abstracts	Surveys		Register data	
		National	Sub-population	National	sub-population
France	12	3	9		
Germany	6	4	2		
Switzerland	5	1	4		
Greece	3		3		
Italy	3		3		
Belgium	2		2		
The Netherlands	2				2
Spain	1		1		
Denmark	1			1	
Slovenia	1				1
Serbia	1		1		
Czech Republic	1	1			


 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

Table A3. Tetanus articles retained from the literature search

Country	No. of abstracts	Surveys		Register data	
		National	Sub-national	National	sub-population
France	16	3	13		
Germany	8	4	4		
Switzerland	5	1	4		
Greece	6		6		
Italy	4		4		
Belgium	2		2		
The Netherlands	3			1	2
Spain	3		3		
United Kingdom	1		1		
Denmark	1			1	
Slovenia	1				1
Serbia	1		1		


	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	114/140

Table A4. Pneumococcus articles retained from the literature search

Country	No. of abstracts	Surveys		Register data		Administered doses		Reimbursement data	
		National	Sub-national	National	sub-national	National	Sub-national	National	sub national
France	10	5	5						
Spain	6		4		2				
Italy 1)	6	2	2	2	2	1			
United Kingdom 2)	6	2	2	3					
Ireland	3	2	1						
Germany	2		1					1	
Portugal	2		2						
The Netherlands	1		1						
Switzerland	1		1						
Greece	1		1						
Norway	1			1					

1) One study reported both national and regional coverage estimates (Zoppi and Trucchi, 2012) another study reported national coverage estimates based on surveys, registers and administered doses (Germinario et al., 2010) and a third compared regional coverage estimates using both survey and register data (Martinelli et al., 2010)

2) One national study compared computer records and self-reports (Mangtani et al., 2007)


	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	115/140

Table A5. Human Papillomavirus articles retained from the literature search

Country	No. of abstracts	Surveys		Register data		Administered doses		Reimbursement data	
		National	Sub-national	National	sub-national	National	Sub-national	National	sub national
France	4		1					1	2
United Kingdom	4		3	1					
The Netherlands	2		1	1					
Italy	2		2						
Germany	2		2						
Greece	2		2						
Belgium	2								2
Denmark	1			1					
Spain 1)	1				1		1		
Switzerland 2)	1						1		

1) In Spain both the number of doses administered and vaccine registers are used to calculate HPV vaccine coverage (Limia et al., 2011)

2) It is not clear if it is subjects vaccinated or administered doses



	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	116/140

Table A6. Influenza articles retained from the literature search




Country	No. of abstracts	Surveys		Register data		Administered doses		Reimbursement data	
		National	Sub-national	National	sub-national	National	Sub-national	National	sub national
France	37	9	25					4	
Spain	37	8	24		4		1		
Italy	17	2	15						
Germany	13	9	4						
United Kingdom									
1)	17	4	8	4	2				
Poland	4	1	1			2			
Ireland	3		3						
Portugal	1	1							
Greece	5	2	3						
The Netherlands	5	3		2					
Sweden	4	2	1		1				
Belgium	2		2						
Switzerland	3		3						
Norway	1			1					
Slovenia	1		1						

1) One study compared register based vaccine uptake with survey-based information


	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	117/140

The following tables show European vaccination schedules for diphtheria, tetanus, pertussis, pneumococcus, human papillomavirus and influenza. These schedules are downloaded for the ECDC homepage <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>.

The colour codes below are used to describe the vaccination schedules

	General recommendation
	Recommendation for specific groups
	Catch-up (e.g. if previous dosed missed)




	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	119/140

**Footnotes:**

- 1: Earliest 6 month after the second dose
- 2: dTaP-IPV every 10 years between 18 and 60 years of age.
- 3: dTaP-IPV every 5 years from 65 years of age
- 4: Subsequent Td booster every 10 years
- 5: only to children born in the period 1990-1995 and previously vaccinated at the age 12 years by sixth dose of dT vaccine.
- 6: Thereafter Td booster every 10 years with or without vaccination against poliomyelitis (IPV) in case of travel to endemic areas and when previous IPV dose was given more than 5 years
- 7: dTdap-IPV or dTT-IPV if last dTdap-IPV received in the previous 5 years
- 8: dTT-IPV every 10 years from 65 years of age
- 9: Booster doses every 10 years. catch-up for those unvaccinated
- 10: Td booster every 10 year. One of the booster dose should be with Tdap or Tdap-IPV. Td from 65 years of age
- 11: Booster dose
- 12: Tdap - Vaccination for pregnant women between 27-36 weeks gestation (introduced in September 2013). If the recipient does not have a medical card, they must pay administration cost
- 13: Subsequent booster doses every 5-10 years
- 14: Subsequent Tdap-IPV booster every 10 years
- 15: should not be given earlier than 5 years after the previous dose
- 16: Td booster every 10 years for adults
- 17: DTacP-IPV at 6 years to begin in 2015
- 18: school-based programme
- 19: Td booster every 10 years
- 20: Subsequent Td booster every 15 years
- 21: One dose at around 65 years of age if primary course completed. For specific courses for catch-up vaccination, please refer to specific recommendations available at
- 22: Either DTacP-IPV or dTdap-IPV can be given depending on availability



	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	121/140

**Footnotes:**

- 1: Earliest 6 month after the second dose
- 2: dTaP-IPV every 10 years between 18 and 60 years of age.
- 3: dTaP-IPV every 5 years from 65 years of age
- 4: Subsequent Td booster every 10 years
- 5: Subsequent booster doses every 10-15 years.
- 6: only to children born in the period 1990-1995 and previously vaccinated at the age 12 years by sixth dose of dT vaccine.
- 6: only to children born in the period 1990-1995 and previously vaccinated at the age 12 years by sixth dose of dT vaccine.
- 8: dTdap-IPV or dTT-IPV if last dTdap-IPV received in the previous 5 years
- 9: dTT-IPV every 10 years from 65 years of age
- 10: Booster doses every 10 years. catch-up for those unvaccinated
- 11: Td booster every 10 year. One of the booster dose should be with Tdap or Tdap-IPV. Td from 65 years of age
- 12: Tdap - Vaccination for pregnant women between 27-36 weeks gestation (introduced in September 2013). If the recipient does not have a medical card, they must pay administration cost of the vaccination out-of-pocket.
- 13: Subsequent booster doses every 5-10 years
- 14: Subsequent Tdap-IPV booster every 10 years
- 15: should not be given earlier than 5 years after the previous dose
- 16: Td booster every 10 years for adults
- 17: DTaP-IPV at 6 years to begin in 2015
- 18: school-based programme
- 19: Td booster every 10 years
- 20: Subsequent Td booster every 15 years
- 21: One dose at around 65 years of age if primary course completed. For specific courses for catch-up vaccination, please refer to specific recommendations available at [http://www.msc.es/ciudadanos/proteccionSalud/vacunaciones/docs/TetanosDifteria\\_2009.pdf](http://www.msc.es/ciudadanos/proteccionSalud/vacunaciones/docs/TetanosDifteria_2009.pdf)
- 22: Either DTaP-IPV or dTdap-IPV can be given depending on availability



 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	122/140

Table A9. Recommended immunisations for pertussis. Source: Vaccine Schedules ECDC





	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	124/140

**Footnotes:**

- 1: Earliest 6 month after the second dose
- 2: For children who received only dTIPV previously
- 3: dTaP-IPV every 10 years between 18 and 60 years of age.
- 4: dTaP-IPV every 5 years from 65 years of age
- 5: Recommended only. One of the booster doses should include pertussis (Td-acp).
- 6: only to children born in the period 1990-1995 and previously vaccinated at the age 12 years by sixth dose of dT vaccine.
- 7: dTdap-IPV or dTT-IPV if last dTdap-IPV received in the previous 5 years
- 8: One of the dTT-IPV booster in adults should be done with a pertussis-containing vaccine as part of the "cocooning" strategy
- 9: Only one of the Td 10-yearly booster doses should be with a Tdap vaccine in adults. Subsequent booster doses are to be done with Td vaccines..
- 10: Td booster every 10 year. One of the booster dose should be with Tdap or Tdap-IPV. Td from 65 years of age
- 11: Booster dose
- 12: Tdap - Vaccination for pregnant women between 27-36 weeks gestation (introduced in September 2013). If the recipient does not have a medical card, they must pay administration cost of the vaccination out-of-pocket.
- 13: After seven years, a low-dose pertussis-containing dT vaccine should be used
- 14: To be given ten years after completing primary vaccination with DTaP-containing vaccines
- 15: Subsequent Tdap-IPV booster every 10 years
- 16: DTaP-IPV at 6 years to begin in 2015
- 17: For more detail on review and recommendation for pertussis vaccination in Spain, please refer to <http://msc.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/TosFerina.pdf>
- 18: Either DTaP-IPV or dTaP-IPV can be given depending on availability
- 19: Specific programme to vaccinate expectant mothers with a pertussis-containing vaccine from 28 weeks of pregnancy. for more information, refer to <http://immunisation.dh.gov.uk/pertussis-pregnant/>



 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	126/140

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring	<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné	<b>Security:</b> CO	127/140

**Footnotes:**

- 1: Earliest 6 month after the second dose
- 2: If no previous vaccination, 1 dose of PPSV23 after one year. If previous vaccination with PPSV23, 1 dose of PCV13 2 years later. If previous dose of PCV13, 1 dose of PPSV23 2 year later.
- 3: catch-up possible until 6 years if previous recommended doses were missed
- 4: vaccines only given on specific indications
- 5: PCV 10 can be replaced with PCV 13, however the cost of PCV 13 is paid by the patient. PCV vaccines can be administered simultaneously with hexavalent vaccine or separately during the first year of life. 3 doses at one month interval.
- 6: PCV 13 also recommended.
- 7: Recommended but not free of charge. for more information, please refer to [http://www.thl.fi/fi\\_FI/web/rokottajankasikirja-fi/pneumokokkikonjugaattirokotukset](http://www.thl.fi/fi_FI/web/rokottajankasikirja-fi/pneumokokkikonjugaattirokotukset)
- 8: number of doses necessary varies according to age
- 9: One dose recommended. Booster only for specific indications
- 10: In previously unvaccinated children or children previously vaccinated with PCV7 or PCV10 vaccine.
- 11: PCV13 + PPSv 23
- 12: Recommended, but not mandatory.
- 13: 1 dose every 10 years (every 5 years for those with conditions putting them at-risk of severe disease)
- 14: The vaccine is free of charge, but administration fees may be charged to patient (based on income and eligibility for free healthcare)
- 15: not part of the basic vaccination plan
- 16: One dose if not vaccinated in the previous 10 years. Reimbursed for some at-risk groups.
- 17: PCV13 can be used. Not free of charge.


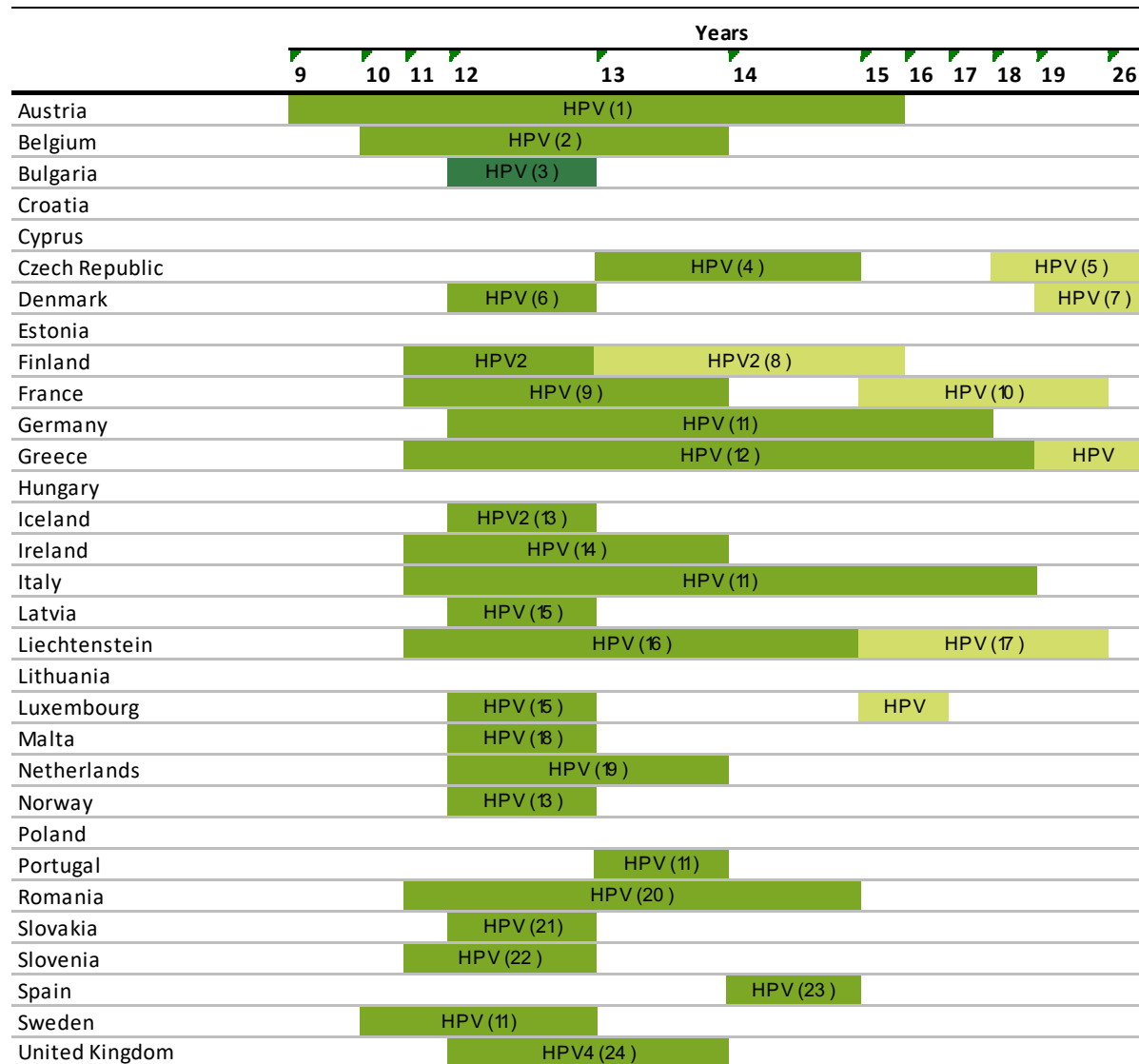

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits			
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final	
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO	128/140

Table A11. Recommended immunisations for human papillomavirus infection. Source: Vaccine Schedules ECDC



	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

**Footnotes:**

- 1: First dose from 9 year of life. catch-up until 50 years.
- 2: recommended for girls 10-13 years old with 3 doses (schedule 0, 1, 6 months (Cervarix®) or 0, 2, 6 months (Gardasil®)
- 3: HPV vaccination is not included in the National Immunization schedule. The vaccination is voluntary, but free of charge for 12-year-old girls.
- 4: Females only. Recommended only.
- 5: Recommended only. Females only. Three doses.
- 6: females only
- 7: Time limited catch-up program for adult women born i 1985-1992. Ends 31 December 2013.
- 8: HPV catch-up during the first 2 years of introduction to girls 13-15 years of age
- 9: Three doses in a 0, 1 or 2, 6 month schedule (girls aged 11 to 14 years)
- 10: Three doses in a 0, 1 or 2, 6 month schedule (girls aged 15 to 19 years)
- 11: Three doses. Females only.
- 12: Females only. Vaccination recommended up to 26 years of age.
- 13: Females only. 7th grade.
- 14: First year second-level school (females 12 to 13 years of age), 3 doses given between 6-12 months.
- 15: Females only.
- 16: Two doses. Females only.
- 17: Females only. catch-up vaccination recommended before the 20th birthday
- 18: For females born from the year 2000 onwards. 3 doses in a 0, 1, 6 month schedule.
- 19: 2014 (January): Change to HPV recommendation. For girls under age 15, Cervarix can be administered in a 2 dose schedule instead of 3 previously. The 0-1-6-schedule in under 15's is replaced by two doses in a 0-6-schedule. Further information for those that are currently completing HPV vaccination is available from [www.prikkenteller.nl](http://www.prikkenteller.nl)
- 20: 3 doses. Recommended, but not mandatory.
- 21: Recommended only. Not included in the national immunization schedule. Partial reimbursement by the national healthcare system.
- 22: girls only
- 23: Three doses. Females only. For more information please refer to <http://www.msssi.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/PapilomaVPH.pdf>
- 24: Females only. Vaccine used: Gardasil.



	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO


Table A12. Recommended immunisations for influenza. Source: Vaccine Schedules ECDC



	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

**Footnotes:**

- 1: Two doses for primary immunisation until the age of 8 years.
- 2: Annual vaccination.
- 3: Annual vaccination. Recommended but not free of charge.
- 4: Vaccines only given on specific indications.
- 5: for more information on the Danish influenza vaccination programme and vaccination of specific at-risk groups, please refer to <http://www.ssi.dk/Vaccination/Influenzavaccination.aspx> (in English, latest recommendations for the 2012/13 season, <http://www.ssi.dk/English/News/EPI-NEWS/2012/No%2039a%20-%202012.aspx>)
- 6: Also recommended for children in specific at-risk groups. One or two doses administered depending on previous influenza vaccination history. Annual vaccination. Funded.
- 7: Annual vaccination. Funded.
- 8: Annual vaccination.
- 9: For specific at risk-groups only.
  
- 10: The vaccine is free of charge, but administration fees may be charged to patient (based on income and eligibility for free healthcare)
- 11: Recommended, but not mandatory.
- 12: Annual vaccination. Recommended, but not mandatory.
- 13: Recommended only. Not included in the national immunization schedule.  
[http://www.ivz.si/cepljenje/strokovna\\_javnost/navodila\\_in\\_priporocila?pi=18&\\_18\\_view=item&\\_18\\_newsid=1316&pl=253-18.0](http://www.ivz.si/cepljenje/strokovna_javnost/navodila_in_priporocila?pi=18&_18_view=item&_18_newsid=1316&pl=253-18.0).
- 15: recommended, not funded except for risk groups; further information on the flu campaign available at [http://www.ivz.si/cepljenje/strokovna\\_javnost/navodila\\_in\\_priporocila?pi=18&\\_18\\_view=item&\\_18\\_newsid=1316&pl=253-18.0](http://www.ivz.si/cepljenje/strokovna_javnost/navodila_in_priporocila?pi=18&_18_view=item&_18_newsid=1316&pl=253-18.0).
- 16: For individuals with certain medical conditions or a weakened immune system, which may put them at risk of complications from influenza.
- 17: - This is defined as children aged two or three years (but not four years) on 1 September 2013  
- The vaccine is given prior to the flu season – usually in September and October
- 18: For individuals with certain medical conditions or a weakened immune system, which may put them at risk of complications from influenza. From 6 months and over.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## Annex II BENEFITS 1: QALY and DALY computation

The most commonly used composite measures of population health are the quality-adjusted-life-years (QALY) and the disability-adjusted life-years (DALY) measures.

The QALY is an adjustment to expected life length (or survival) for the quality of life experienced; it is calculated as the amount of time lived in a disabling state of health, weighted by the quality of life in that state (the utility weight). A utility weight represents the valuation attached to a particular health state, with zero equivalent to death and one representing perfect health.

$QALY = \sum_{i=1} u_i \times t_i$  (utility weight for health state  $i \times$  time spent in state  $i$ , summed over all states)

Expected improvements to health from an intervention (i.e., the benefits of treatment, vaccination, or screening) correspond to positive QALYs. One QALY would be produced by an intervention that ensured perfect health for one additional year.


The difference between the two measures is subtle; one can be viewed as the inverse of the other. The DALY measures health loss and therefore is ideally minimal; the QALY measures health gain, as equivalent healthy years lived, and therefore should be maximised. The positive effect of an intervention is correspondingly reported differently between the two measures: DALYs averted vs. QALYs gained. All SMPH involve social value choices to be made (to specify the utilities or disability weights associated with a health-reducing condition). For the QALY, utility weights have usually been elicited from panels of patients or lay persons; for the DALY, weights are derived using experts. Techniques for weight elicitation include time-trade-off and standard gamble methods. Differences in the weights elicited, and in the use of life expectancy values between the two measures (population averages for the DALY; frequently based on clinical studies for the QALY), mean that in practice the DALY cannot simply be considered as an inverse QALY (66).

Although both QALYs and DALYs are suitable choices for assessing the benefits of vaccines, the following discussion focusses on the DALY measure.

### *DALY computation*

The estimation of disease burden using DALYs requires a number of data sources, including incidence or prevalence data (often available from statutory notification systems), severity weights and durations. One approach to DALY computation is to collect incidence (or prevalence) data for all health states associated with a disease; the other is to define outcome trees (which detail the various health states and how they are related within a disease's natural history). The latter approach also requires information on the transition probabilities describing the rate of progression between health states

The DALY for a given health state is the simple sum of two components: (i) premature mortality, quantified as the number of years of life lost (Years of Life Lost = YLL) due to

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

dying prematurely, and (ii) morbidity, the number of years lived (at less than full health) in that health state (Years Lived with Disability = YLD). The DALY for a disease is therefore the sum (iii) of the YLL and YLD associated with all health states specified within the disease's natural history.


(i)  $YLD = I \times DW \times D$  (incidence  $\times$  disability weight  $\times$  duration)

(ii)  $YLL = N \times LE$  (number of deaths  $\times$  remaining life expectancy)

(iii)  $DALY = YLL + YLD$

For infectious diseases, DALY calculation can be carried out by considering as a starting point either the pathogen or the associated health state(s) (which could have been caused by more than one pathogen). If the pathogen is taken as a starting point, the focus of burden calculation is on all health states (possibly long-term) that can be causally attributed to a specific pathogen. If the health state rather than the pathogen is in focus, then the burden associated with that health state is of interest, and the cause is not necessarily important. The YLD component of the DALY measure can be calculated using either prevalence or incidence data collected from the specific population of interest. In the latter case, all new cases of a particular disease are counted, and the burden associated with all future health states that potentially follow initial infection is included. Working with incidence data gives a better understanding of the possible future health gains expected from prevention initiatives that reduce the incidence of infection.

If we take measles as an example and use the pathogen- and incidence-based approach to compute DALYs (44), the first step is to create an outcome tree and specify the transitional probabilities between health outcomes. One of the possible outcomes leading from symptomatic measles infection is the rare sequela subacute sclerosing panencephalitis (SSPE). If SSPE develops in measles-infected infants <1 year old with a risk of 0.008%, and the disability weight for SSPE is 0.93 and the duration of illness is 2 years, then the YLD calculated for 1000 infected cases is  $(1000 \times 0.00008 \times 2) = 0.16$ . Given that SSPE is fatal, the YLL calculated for this infected population (assuming age 2 years at death and a remaining life expectancy at age 2 years of 78 years) is  $(1000 \times 0.00008 \times 78) = 6.24$ . The total DALYs for this age group due to SSPE only is therefore estimated at 6.40. YLD and YLL for all other health outcomes defined for measles would be calculated similarly and summed to give the estimated total burden due to measles.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## Annex III ADVANCE dossier for review of methods to assess benefits


### A. Introduction of Men B in the UK national immunisation programme

#### Background on Men B vaccine (1)

- The four-component meningococcal serogroup B vaccine (4CMenB; Bexsero, Novartis) is the first successful vaccine against serogroup B meningococcal disease. The vaccine has been approved by licensing authorities in Europe, Canada, and Australia.
- JCVI considered the use of 4CMenB in the UK immunisation programme in a JCVI subgroup and in several JCVI meetings.
- During the last JCVI meeting on this topic (11-12 Feb 2014) JCVI concluded that (2):
  - 4CMenB would not be cost-effective for the NHS at the current UK list-price for any age group;
  - an infant 4CMenB vaccination programme could be cost-effective for infants in a four-dose schedule (at age 2, 3, 4, and 12 months), but only if the vaccine price was very low;
  - cost-effectiveness could be improved by using a three-dose schedule (at age 2, 4, and 12 months);
  - removing the dose of meningococcal C vaccine at age 3 months would reduce the financial burden of an infant immunisation programme using 4CMenB, and would be possible considering 4CMenB could cover some strains of capsular group C meningococcus;
  - in some scenarios adolescent vaccination with 4CMenB was cost-effective. However, the burden of disease caused by capsular group B meningococcus is low in teenagers, and so the cost effectiveness of adolescent vaccination would be highly dependent on the vaccine inducing long-term protection against disease in vaccinees and carriage of strains of capsular group B meningococcus, a characteristic which is highly uncertain.
- Based on this, JCVI recommended to the Department of Health
  - to plan the implementation of a 2, 4, and 12 month (2+1) infant immunisation programme with 4CMenB, subject to procurement at a cost-effective price;
  - to remove the 3-month dose of capsular group C meningococcal vaccine from the schedule subject to the effective implementation of the group C meningococcal adolescent booster programme.

#### Evidence available to the JCVI

- *Safety and immunogenicity data from clinical trials:*
  - Vesikari et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet* 2013; 381: 825–35 (3).
  - Gossger et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 2012; 307: 573–82 (4).

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

- Santolaya et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observerblind, placebo-controlled study. *Lancet* 2012; 379: 617–24 (5).
- *In-vitro studies assessing the proportion of strains of capsular group B meningococcus currently circulating in the UK that is potentially covered by 4CMenB:*
  - Frosi et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 2013; 31: 4968–74 (6).
- *Mathematical modelling and economic analyses:*
  - Christensen et al. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine* 2013; 31: 2638–46 (7).
  - Repeated economic analyses with updated assumptions (not published yet) and an independent review by the University of Warwick.

**Task: Assessment of methods used to generate the evidence on benefits of 4CMenB considered by JCVI**

- You are asked to review the methods used to generate the evidence on benefits of 4CMenB. Since cost-effectiveness is explicitly **not** part of Advance, the specific cost-effectiveness methods do not need to be assessed.
- The methods used are:
  - Clinical trial (reference 3, 4, 5)
  - Laboratory assessment of strain coverage by 4CMenB (reference 6)
  - Mathematical modelling (reference 7). In addition to effectiveness, this study also assessed cost-effectiveness. As outlined above, this specific part does not need to be assessed.

**Criteria to assess methods**

The criteria to assess methods which were specified in the advance WP4 report on benefits are listed below. They can be used to assess methods for each scenario, but this is not necessary.

**1. Statistical criteria.**


These comprise things like power to detect an effect; finite sample bias of the effect estimator; and efficiency of the effect estimator. Also included may be issues relating to Type I error probabilities or false discovery rates for multiple testing.

**2. Temporal criteria.**

These cover the time to detection or confirmation of an effect, for various specifications of the Type I error probability (or average run length), and also the frequency with which and the speed at which results can be updated. Also perhaps how quickly various study designs can be implemented.

**3. Robustness criteria.**

These cover robustness to measured and unmeasured confounding; assumptions required and robustness to model mis-specification; robustness to misclassification of exposure and disease; and dependence on data types.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

#### 4. Operational criteria.

These cover issues such as data requirements, data cleaning or checking requirements, complexity of implementation, and financial cost.

#### 5. Ethical criteria

These cover issues such as ethical limitations in withholding a (moderately) effective vaccine from a population for research purposes only.

#### References

1. Pollard AJ1, Riordan A2, Ramsay M3. Group B meningococcal vaccine: recommendations for UK use. *Lancet*. 2014 Mar 29;383(9923):1103-4.



Pollard 2014.pdf

2. Minutes of JCVI meeting dd 11-12 Feb 2014.



Minute of February  
2014 meeting of JCVI

3. Vesikari et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet* 2013; 381: 825–35 (3).



Vesikari 2013.pdf

4. Gossger et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 2012; 307: 573–82 (4).




Gossger 2012.pdf

5. Santolaya et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observerblind, placebo-controlled study. *Lancet* 2012; 379: 617–24 (5).



Santolaya 2012.pdf

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

6. Froisi et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 2013; 31: 4968–74 (6).




Frosi 2013.pdf

7. Christensen et al. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine* 2013; 31: 2638–46 (7).



Christensen  
2013.pdf

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

## B. Withdrawal of Hexavac by the EMEA in 2005

### Background (1,2)

- On 23 October 2000, the European Commission issued a marketing authorisation valid throughout the European Union for the medicinal product Hexavac (diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, hepatitis b (recombinant) and haemophilus influenzae type b conjugate vaccine, adjuvanted). The marketing authorisation holder (MAH) for Hexavac was Sanofi Pasteur MSD, SNC.
- On 17 November 2005, the European Commission suspended the marketing authorisation on the recommendation of the Agency’s Committee for Medicinal Products for Human Use (CHMP) further to the CHMP’s review of the short and long-term protection afforded by recombinant hepatitis B vaccines.
- The concerns over the immunogenicity of the HepB component increased when lower than expected seroconversion rates were observed following the concomitant administration of Hexavac with other meningococcal and pneumococcal vaccines (3).
- Additional concerns were raised by the recent finding that children primary immunised with Hexavac apparently respond to a booster dose of a monovalent Hepatitis B vaccine as a function of the geometric mean titres (GMTs) achieved upon completion of the primary immunisation series. Infants with an initial immune response between 10 and 100 mIU/ml anti HBsAg responded less efficiently or not at all to a single dose of monovalent Hepatitis B vaccine given at the age of 7-9 years, compared to those with initial titres between 100 and 1000 mIU/ml. These findings were based on a rather limited number of infants but raised concerns because the findings of a challenge ‘weaker’ than priming with or without booster dose are unexpected.
- The European Commission was notified by a letter dated 11 April 2012 of the MAH’s decision to voluntarily withdraw the marketing authorisation for Hexavac for commercial reasons. Hexavac has not been marketed in any EU country since the suspension in 2005.
- On 28 June 2012, the European Commission issued a decision withdrawing the marketing authorisation for Hexavac.

### Evidence available to the EMEA to withdraw the marketing authorization for Hexavac


- Tichmann et al. Comparison of the immunogenicity and reactogenicity of two commercially available hexavalent vaccines administered as a primary vaccination course at 2, 4 and 6 months of age. Vaccine. 2005 May 9;23(25):3272-9. (3)

### Task: Assessment of methods used to generate the evidence on benefits of Hexavac considered by the EMA

- You are asked to review the method used to generate the evidence to withdraw the market authorization for Hexavac.
- The method used is a ‘head-to-head’ randomized trial with Hexavac and Infanrix hexa (3).

### Criteria to assess methods

The criteria to assess methods which were specified in the advance WP4 report on benefits are listed below. They can be used to assess methods for this scenario, but this is not necessary.

	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO

### Statistical criteria.

These comprise things like power to detect an effect; finite sample bias of the effect estimator; and efficiency of the effect estimator. Also included may be issues relating to Type I error probabilities or false discovery rates for multiple testing.

### Temporal criteria.

These cover the time to detection or confirmation of an effect, for various specifications of the Type I error probability (or average run length), and also the frequency with which and the speed at which results can be updated. Also perhaps how quickly various study designs can be implemented.

### Robustness criteria.

These cover robustness to measured and unmeasured confounding; assumptions required and robustness to model mis-specification; robustness to misclassification of exposure and disease; and dependence on data types.

### Operational criteria.

These cover issues such as data requirements, data cleaning or checking requirements, complexity of implementation, and financial cost.

### Ethical criteria

These cover issues such as ethical limitations in withholding a (moderately) effective vaccine from a population for research purposes only.

1. European Medicines Agency. Public statement on Hexavac [diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, hepatitis b (recombinant) and haemophilus influenzae type b conjugate vaccine, adjuvanted] Withdrawal of marketing authorisation in the European Union. EMA/273279/2012 24 July 2012.



EMA Hexavac.pdf

2. European Medicines Agency. Scientific conclusions and grounds for the suspension of the marketing authorization of Hexavac, 2005




EMA  
Hexavac\_scientific gr

3. Tichmann et al. Comparison of the immunogenicity and reactogenicity of two commercially available hexavalent vaccines administered as a primary vaccination course at 2, 4 and 6 months of age. *Vaccine*. 2005 May 9;23(25):3272-9. (3)



Tichmann 2005.pdf

 <b>ADVANCE</b> IMI - 115557	<b>D4.1</b> Report on appraisal of methods for vaccine coverage, burden of disease and vaccine benefits		
	<b>WP4.</b> Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit risk monitoring		<b>Version:</b> v2.0 – Final
	<b>Author(s):</b> Hanne-Dorthe Emborg, Susan Hahné		<b>Security:</b> CO