Summary

Introduction (part 1)

During the previous century, highly effective vaccines have been developed which allow primary prevention of infectious diseases that once disabled or killed large numbers of adults and children, such as smallpox, polio and diphtheria. Using these vaccines in a universal program that targets the susceptible (childhood) population as a whole has resulted in elimination of some infectious diseases, as could be predicted from the herd immunity concept, and in impressive disease reduction of other infectious diseases since many years. Nevertheless, continued and extensive surveillance is needed since re-introduction remains possible and can be induced by program performance regression or failing vaccine-induced immunity.

To assess the impact of the immunization program on population immunity and to guide decisions on adaptation of the existing program or inclusion of new vaccines, accurate information on vaccine uptake as well as on remaining susceptibility, with their determinants, is highly needed.

This PhD thesis/dissertation comprises information obtained from two vaccination coverage surveys in Flanders (in 2005 and 2008) as well as from two serological surveys performed in Belgium as a whole (in 2002 and 2006). These two types of surveys assess different aspects of immunization program implementation and achievements. In addition similarities between findings with respect to the level of protection against vaccine-preventable diseases achieved in Flanders were evaluated.

Studies presented in this dissertation

The design of both types of surveys was cross-sectional and retrospective, they thus reflect events further in the past together with more recent events and achievements. Therefore, historical information on program changes over time which could impact on the current serological profile, vaccine uptake and policy was addressed first (**Part 2**).

Next, in **part 3**, we present the information obtained through two serial immunization coverage surveys performed in 2005 and 2008, which were limited to children living in Flanders since they were both ordered by the Flemish Ministry of Health, Welfare and Family. Their main aim was to assess coverage of recommended vaccines available free of charge, i.e. poliomyelitis (polio), diphtheria-tetanus-pertussis (DTP), *H influenzae* type b (Hib), hepatitis B (HBV), measles-mumps-rubella (MMR), conjugate pneumococcal (PCV-7)

and meningococcal (MenC) vaccines. Each survey comprised a random cluster sample of 18- to 24-month-old toddlers and one of 13- to 14-year-old adolescents; the 2005 survey was extended with an additional sample of 7- to 8-year-olds. The results were analyzed in terms of uptake of recommended vaccines in different age groups along with its age-specific predictors, catch-up vaccination after infancy, and age-specific involvement of different vaccinators (chapters 3.1-3.4). Compliance to age recommendations for Hib and pertussis vaccines in infancy, its evolution since 1999, and its predictors were additionally assessed (chapter 3.5); as well as the amount of parental work-loss for infant vaccinations, and parental attitudes with respect to concomitant vaccine injections for infants of adolescents, (chapter 3.6).

The third aim was to evaluate current population immunity, through two serial serological surveys performed in residual sera of 1-65 year-olds collected at two different time-points In 2002, an age-stratified and geographically representative sero-survey was performed in Belgium allowing participation to the European Sero-Epidemiology Network 2 EU-project (ESEN2)(2001-2004). To continue this serological surveillance, a similar sero-survey was performed in 2006. The laboratory analysis of both sero-surveys was performed with commercial ELISA assays at the Institute of Public Health in Brussels. Within part 4 of this dissertation, the age-specific antibody profile for measles, rubella and hepatitis B at both time-points and for mumps, diphtheria and tetanus in 2006 are presented, and the predictive effect of a limited number of other characteristics (mainly region of residence and gender) was evaluated.

Results

The results illustrate the value of vaccine coverage and serological surveillance for the evaluation and guidance of the immunization program.

Vaccine uptake in Flanders was found to be higher in 2008 compared to 2005, and higher at infant age (where it surpassed 90% for all assessed vaccines except pneumococcal, and even 95% for MMR in 2008) than at later ages (where the coverage of most recommended vaccines was below 90%). Note that loss of vaccination documents was also more frequent at later ages, and could thus have biased these findings. Compliance to age recommendations in infancy increased as well, but delay with successive doses should further be avoided for optimal prevention of severe infant pertussis. In 2008, only 65% of infants received a third dose of pertussis-containing vaccine within 4 weeks after reaching the recommended age (4 months). The survey in 7 year-olds indicated that some catch-up

for MMR1 and HBV had happened after infancy and had added 5% and 6%, respectively, to their coverage in this age cohort.
Coverage of doses needed later in childhood, i.e. polio 5, DT(P)5, and MMR2, was suboptimal. The uptake of HBV vaccination in adolescents (89% in 2008) (catch-up part of the campaign) was clearly lower than in infancy (95% in 2008) as well. Analysis for predictors of vaccine uptake suggest, in general, a need to support vaccinating activities of private vaccinators, and to develop specific supporting strategies for large families and families in an unfavorable socio-economic situation, as well as for children in special education. Any interventions to increase vaccine uptake in infants should address both the importance of timely administration and completion of the schedule, since similar risk factors were found for delayed as for incomplete vaccination.
An additional item in the 2005 survey demonstrated that parental work-loss for infant vaccinations was rare, and that parents of young children as well as those of adolescents preferred a maximum of two vaccine-injections to be given concomitantly.

The serological results presented in part 4 should be interpreted with caution since they cannot provide absolute proof of protection or susceptibility, but they suggest that in Belgium measles immunity in children and young adults (5-24 year-olds in 2006) is insufficient to achieve elimination, that rubella immunity in women at fertile age is insufficient to fully prevent congenital rubella syndrome (below protective titer in 15%), and that mumps outbreaks in adolescents and adults could occur (chapter 4.4). Within the European comparison performed through the ESEN2 project (chapters 4.1 and 4.2), seronegativity for measles and rubella in childhood, and prevalence of non-protective rubella titers in women at childbearing age, were higher in Belgium than in the majority of the other participating countries. These findings stress the need to enhance coverage of MMR2 at the recommended age (10-13 years) as well as after adolescence (by catch-up programmes), and to systematically offer rubella-screening to pregnant women, or even better at pre-conception, in order to vaccinate any seronegatives.
The HBV sero-profile of 1-19 year-olds, and its evolution from 2002 to 2006, confirms the high HBV-coverage found in recent coverage surveys, and illustrates the increasing coverage since the gradual implementation of universal HBV vaccination in the late nineties of the previous century (chapters 4.3 and 4.5). But the findings also illustrate the limitations for estimating HBV coverage from serological surveys for cohorts vaccinated further in the past. The data for markers of HBV infection indicate that prevalence of HBV has remained unchanged (at 2%) since universal vaccination was implemented.

A straight-forward comparison of serological and coverage data for MMR, HBV and diphtheria in birth cohorts from Flanders that were assessed with both types of surveys was reassuring, though serological data were limited (chapter 4.6).

For diphtheria and tetanus, the serological results demonstrate that replacing the adolescent T booster by dT has enhanced immunity in the 15-25 years age cohorts, but the further dT booster policy is reaching adults older than 40 insufficiently. The lowest level of seroprotection against diphtheria was found in 55-59 year-olds (20%) and against tetanus in 60-65 year-olds (80%) (chapter 4.5).
Some regional and gender effects, mostly predictable from historical region or gender-related differences in vaccine availability, or acceptance, could be identified (chapters 4.4 and 4.5). Females were at higher risk for tetanus. Regional differences in seronegativity were found for hepatitis B, due to differences in vaccine uptake, and to a lesser extent for mumps and rubella, though population immunity is suboptimal in each region. This situation could be improved mainly by endorsing the existing catch-up possibilities for both MMR doses, and by continuing targeting adults in at-risk professions or attitudes for hepatitis B through tailored immunization programmes. The dTpa cocoon strategy could be a good opportunity to enhance protection against diphtheria and tetanus, next to pertussis, in older adults who have grandchildren; though more efforts are needed to reach the older adult age group. Concerted actions from different health providers as well as health-related institutions, as promoted by the yearly European Immunisation Week, can support this aim.

In the **discussion and conclusion** (part 5) we further state that regular re-assessments of coverage and seroprevalence would provide the opportunity to detect and interpret trends of population immunity in time, as illustrated within this thesis. Moreover it would allow for cross-validation of results, taking into account the limits of each method in estimating immunity.
Within a larger perspective of comprehensive immunization program surveillance, endorsement of surveillance of vaccine preventable diseases and their prevention programmes (through clinical and laboratory monitoring, coverage surveys and vaccino-vigilance) would allow improving guidance and monitoring of the immunization programs in Belgium and hence increase their effectiveness.