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（様式９）

学位論文内容の要旨

博士の専攻分野の名称　　博士（医　学）　　氏 名　　木下　諒

学 位 論 文 題 名

Towards an assessment framework for herd immunity against vaccine preventable diseases

（ワクチン予防可能疾患の集団免疫度に関する評価体系の提案）

【Background】

In Japan, routine immunization against rubella and measles has been implemented since 1976 and 1978 respectively. For rubella, Japan initially targeted women aged from 12 to 15 years as vaccines, aiming to individually protect women who were at risk of having a fetus with congenital rubella infection, which may lead to congenital rubella syndrome (CRS). From 1995, the vaccination policy shifted, targeting both genders aged after reaching the age of 1, to elevate and maintain herd immunity. For measles, routine vaccination was introduced in 1978, targeting both genders. Only a single dose of attenuated monovalent vaccine was implemented until the second dose regimen initiated against birth cohorts born in and after 1990. Both rubella and measles have yet to be under full control in the country due to insufficient herd immunity, and chains of transmission are frequently observed in the present day. A fundamental path to accurately control vaccine preventable diseases is to evaluate the herd immunity level or to estimate the reproduction number, *R*. The present dissertation consists of two case studies that assess herd immunity levels of rubella (chapter 1) and measles (chapter 2), respectively, in Japan.

【Methods】

Chapter 1 (Rubella): Seroepidemiological data, vaccination coverage data, and demographic statistics were utilized to estimate the proportion susceptible against rubella in the country. Seroconversion was defined as an HI titer ≥32. Susceptible pockets were identified by spotting various types of cohort (e.g. birth cohorts) below the herd immunity threshold ($1-1/R_0$). The herd immunity threshold for rubella was 83.6% assuming that the R_0 of rubella is 6.1. The age-standardized seronegative proportion, and the absolute number of live births at risk of developing CRS was calculated as a function of time to assess herd immunity against rubella at the population level.

Chapter 2 (Measles): Seroepidemiological data of unvaccinated individuals, vaccination coverage data, and demographic statistics were utilized to estimate to quantify the age-dependent immune fraction against measles in the country. Baseline cutoff value for seroconversion of PA titers was defined as 1:128 (Yoden index = 0.965), and 1:256 (Yoden index = 0.950) was also examined as an alternative. The herd immunity threshold for measles was 90-95% assuming that the R_0 of measles is 10-20. Immunity acquired by natural infection and vaccination was separately inferable by utilizing seroepidemiological data of unvaccinated individuals, and vaccination coverage data. The second dose was interpreted in two different scenarios, i.e., booster and random shots. The effective reproduction number (R_e), the average number of secondary cases generated by a single infected individual, and the age at infection were explored using the age-dependent transmission model and the next generation matrix.

【Results】

Chapter 1 (Rubella): Due to heterogeneities in the susceptible fraction across age and gender, transmission chains of rubella is continuing, fueled by insufficient herd immunity among adult male. Susceptible pockets were identified in adult male for rubella, because the male cohorts remained unimmunized by the present day. Notable susceptible pockets were identified by graphing the seroprevalence by birth years, which found cohorts born from 1974 to 1978 and 1989 to 1993 at low seroprevalence levels below 83.6% (herd immunity threshold). A minor susceptible pocket in those born from 1989 to 1993 was observed in the female population. In 1982, the median (and IQR) age of reported cases was 7 (2.5–7.0) years, among both males and females. The median (25–75th centiles) age in 2014 was elevated to 32.0 (17.0–42.0) years among males and 27.0 (7.0–37.0) years among females. While the seronegative proportions in 1983 were 45.7% (95% CI 32.5% to 58.9%) and 35.6% (95% CI 31.2% to 40.0%) among males and females, respectively, the proportions decreased in 2013 to 18.3% (95% CI 16.8% to 19.8%) and 15.6% (95% CI 10.0% to 21.2%). The number of susceptible live births in 1983 was calculated as 171 875, which was reduced to 23 697 in 2013.

Chapter 2 (Measles): Due to insufficient immunization among working-age adults, transmission chains of measles is maintained in the country even after the verification of local elimination of measles in 2015. If the second dose completely acted as a booster, a proportion immune above 90% would be achieved only among those aged 5 years or less in 2016. Alternatively, if the second dose was randomly distributed, a proportion immune over 90% would be achieved among those aged under 25 years. In 2016, adopting R_0 to be the minimum value of 10 and following scenario 1, R_v was estimated to be 1.50 and 1.57 for cutoff values of 1:128 and 1:256, respectively. Similarly, following scenario 2, R_v was estimated as 1.50 and 1.52, respectively, using the abovementioned cutoff values. If the latest vaccination policy were to continue to 2025, R_v would be 1.50 and 1.39 for scenarios 1 and 2, respectively, assuming R_0 is 10. The R_0 was estimated well above 1 from 2016 to 2025 for all assumed values of R_0. In 1983, the median (and interquartile) age of notified measles cases was 3.0 (3.0–3.0) years; in 2016, the median (25–75th centiles) age had increased to 27.0 (17.0–32.0) years.

【Discussion】

The present dissertation assessed the herd immunity against rubella and measles in Japan. Age and gender dependent risk groups can be identified by analyzing serological surveillance and vaccination coverage data and using mathematical models. Mass vaccination lessens the force of infection and may lead to an elevated age at infection; therefore, it is essential to attain sufficient vaccination coverage to achieve herd immunity especially for rubella, in order to prevent infections among pregnant women. Identifying the susceptible population is beneficial to plan supplementary immunization programs for attaining the local elimination.

【Conclusion】

The present dissertation comprehensively demonstrated an elevated age at infection with rubella and measles, and the presence of susceptible pockets, especially among adults. Although the large oscillating outbreaks may be over, the country will be prone to rubella and measles outbreaks following importations of the diseases. I believe that my series of studies have successfully shown that supplementary immunization can be objectively planned to construct herd immunity against rubella and measles in Japan.