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Meta-analysis of vaccine effectiveness of mumps-containing vaccine under different immunization srategies in China

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ABSTRACT

Objective: To evaluate vaccine effectiveness (VE) of mumps-containing vaccine (MuV) under different immunization strategies.
Methods: We conducted Medline, Embase, China National Knowledge Internet (CNKI), and Wan Fang Database (WF) searches for Chinese and English language articles describing studies of mumps VE in a Chinese population. Evaluated articles were scored on quality using the Newcastle–Ottawa Scale. Meta-analysis was conducted using random effects models. Sensitivity analysis, subgroup analysis and meta-regression were conducted to explore heterogeneity.
Results: A total of 32 studies in 19 papers were included; 14 were case-control studies, and 18 were cohort studies. Half of the studies were of high quality; 41% were of moderate quality. The overall VE for mumps containing vaccine (either one dose or two doses) was 85% (95% CI 76–90%) for cohort studies and 88% (95% CI 82–92%) for case-control studies. Using random effects meta-regression we found significant differences in some study covariates; for instance, VE varied by population (VE = 88% in day care versus 69% in pupil, $p = 0.008$) and emergency versus routine immunization (VE = 80% for routine immunization versus 95% for emergency immunization, $p = 0.041$). However, these results must be interpreted with caution due to the low number of studies in subgroups, with the permutation test giving non-significant results that indicated that the results may be due to chance.
Conclusions: MuV provides good protection from mumps infection. Further studies of mumps VE with larger sample sizes enabling subgroup analyses will be needed to confirm our findings.

1. Introduction

Mumps is caused by mumps virus (MuV) and is an acute respiratory infectious disease with worldwide distribution. In 1990, the China government made mumps a notifiable disease [1]. In 2004, the China immunization program began conducting case reports using a web-based, real time reporting system [2]. Reported incidence rates have been approximately 22 per 100,000 total population, but the incidence rate was as high as 89.91 per 100,000 in 2009 in one province [3–7]. The number of reported mumps outbreaks was 436, 327, and 194 for 2008, 2009, and 2010, respectively [3]. Because of the many outbreaks and high incidence rates, it is important to strengthen and improve mumps prevention and control in China.

Mumps vaccine (MuV) is known to be the most effective way to prevent mumps. In the 1950s, countries began to develop live attenuated mumps vaccine based on the Jeryl Lynn strain, the RIT4385 strain, the Leningrad-3 strain, and the Urabe and L-Zagreb strains [8]. In China, mumps vaccine has been produced by the S79 strain, which was derived from the US Jeryl Lynn strain and attenuated by three passages in chicken embryo cells in 1979. Shanghai, Beijing, and Lanzhou Institutes of Biological Products have been allowed by the Ministry of Health to produce S79 mumps vaccine since 1990 [9]. Currently, three types of mumps-containing vaccine are used in China: monovalent mumps vaccine, measles–mumps (MM) vaccine, and measles–mumps–rubella (MMR) vaccine. However, reported vaccine effectiveness (VE) of mumps containing vaccines has varied substantially. North America and many European countries have reported VE of Jeryl Lynn strain mumps vaccine in their countries (VE 79%, range 62–91%) [10], but there are relatively few China MuV VE data available in the international literature.

Measles, mumps, and rubella immunization strategies and schedules vary by country. The China Expanded Program on Immunization recommends MR (Measles and Rubella Combined Vaccine) at 8 months of age and MMR at 18–24 months of age, which

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provides one routine dose of mumps vaccine. However, the China program has not completely developed its mumps immunization strategy. We conducted this meta-analysis to evaluate VE of mumps vaccines and to help provide a scientific basis for improvement of mumps immunization strategies.

2. Methods

2.1. Literature search

To identify all studies that assessed the efficacy or effectiveness of mumps vaccine in Chinese population, we searched China National Knowledge Internet (CNKI) (through February, 2012) and the Wan Fang Database (WF) (from 1980 through February 2012) using key words "mumps" and "vaccine." We also searched PubMed (through February 2012), EMBASE (through February 2012) and the Cochrane Library. Searches were limited to articles in English and Chinese. We scanned reference lists and conducted manual searches in some relevant journals, such as the *Chinese Journal of Vaccines and Immunization and Vaccine*. We also contacted authors when necessary.

2.2. Inclusion and exclusion criteria

We included published studies assessing the efficacy or effectiveness of the mumps vaccine among healthy Chinese individuals, regardless of dose amount, type of mumps vaccine, and vaccination schedule. Randomized controlled trials (RCT), case-control studies, cohort studies, and other observational studies were included in the search. Studies of methodology, molecular biology, vaccine development, animal studies, popular science lectures, newspaper articles, and literature reviews were not included in this analysis. We considered multiple reports of a single study and duplicate publications as one study. For the articles describing the same study, but published in both English and Chinese, we selected the article with the most complete information. Included studies had to have a comparison group that received a placebo or a non-mumps vaccine, and had to provide sufficient data to determine mumps incidence, vaccination rate, or relative risks/odds ratios (RR/OR) and 95% CI.

2.3. Data extraction

From each study, we collected information that might influence efficacy or effectiveness of mumps vaccine. We extracted the following information onto prepared templates: authors, year of publication, study year, journal, study design, age of subjects, sample size, number of vaccine doses, type of vaccine (monovalent or combined; domestic or imported) in the case and control groups, and RR/OR value and 95% CI.

2.4. Methodological quality or validity assessment

The methodological quality of each included studies was assessed using the Newcastle-Ottawa Scale (NOS) [11]. This scale consists of nine items categorized into three groups—selection, comparability, and outcome/exposure—for evaluating observational studies with meta-analysis. NOS assigns a maximum of nine points to each study. Studies with scores of 1–3, 4–6, and 7–9 were considered as low, intermediate, and high quality, respectively.

2.5. Statistical analysis

We used Stata (version 11.0) to perform all statistical calculations in this meta-analysis. We calculated relative risks (RR) for cohort studies and odds ratios (OR) for case-control studies. Data were combined, and pooled estimates of RR/OR were calculated using random effects models. Vaccine effectiveness was defined as: $VE = (1 - RR) \times 100\%$, and similarly for the OR. The chi-square test was used to estimate heterogeneity; we considered a p value <0.10 as being significant. Since cohort study and case-control study are two different types of study method and they have different levels of evidence, pooled estimates of RR and OR were presented separately. Sensitivity analyses were conducted based on NOS score (studies with score >3 were included). We conducted subgroup analyses with a random effect model to explore potential sources of heterogeneity according to these factors in case-control study and cohort study: (a) emergency/routine immunization, (b) population (pupil, day-care student), (c) doses (one dose, two doses), (d) domestic/imported vaccine, (e) monovalent/combined vaccine. In addition, we also performed random effects meta-regression to analyze above factors. Because cohort studies provide more reliable evidence than case-control studies and reported more information on study characteristics, we examined potential sources of heterogeneity in cohort studies via meta-regression. The covariates of statistical significance (p value < 0.1) in single covariate analyses were then included in subsequent multiple meta-regression. To avoid false positive results, we applied permutation test approach to obtain an adjusted p value. We assessed publication bias by Beggs funnel plots.

3. Results

3.1. Search results

We identified a total of 432 papers from the literature search; 408 duplicate or irrelevant publications were excluded after reading the titles and abstracts. We also excluded five articles that did not provide sufficient data or did not fulfil other criteria. Studies in the same article with different designs, vaccine types, or population groups were determined to be different studies. The remaining 19 articles, involving 32 studies, were included.

3.2. Study characteristics

Of the 32 studies, 14 were case-control studies and 18 were cohort studies. Twenty-eight studies evaluated routine immunization, and four evaluated emergency response immunization. Among the cohort studies, eight included subjects aged 3–6 years (day-care group), and six included subjects 7–15 years of age (pupil group); 13 studies referred to one dose and one study referred to two doses. Among case-control studies, eight referred to domestic vaccine and two to imported vaccine. Seven studies referred to monovalent vaccine and three to combined vaccine. Ten studies referred to one dose and one referred to two doses (Table 1). According to the NOS, the overall median quality score was 6.5 (IQR 5–8). Sixteen studies (50%) were of high quality; 13 studies (40.6%) were of intermediate quality; and three studies (9.4%) were of low quality (Table 2).

3.3. Meta-analysis of vaccine effectiveness [9,12–29]

Among cohort studies, there was statistically significant heterogeneity ($\chi^2 = 116.41$, $p < 0.001$). Pooled estimates of RR (0.15, 95% CI 0.10–0.24; 18 studies) were calculated using a random effects model. The pooled VE was 85% (95% CI 76–90%; 18 studies). Among case-control studies, there was large heterogeneity ($\chi^2 = 49.43$, $p < 0.001$). We used a random effects model to calculate the pooled OR (0.12, 95% CI 0.08–0.18; 14 studies). The pooled VE was 88% (95% CI 82–92%; 14 studies) (Fig. 1).