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Review

A systematic review of human-to-human transmission of measles vaccine virus

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ABSTRACT

Measles is one of the most contagious human diseases. Administration of the live attenuated measles vaccine has substantially reduced childhood mortality and morbidity since its licensure in 1963. The live but attenuated form of the vaccine describes a virus poorly adapted to replicating in human tissue, but with a replication yield sufficient to elicit an immune response for long-term protection. Given the high transmissibility of the wild-type virus and that transmission of other live vaccine viruses has been documented, we conducted a systematic review to establish if there is any evidence of human-to-human transmission of the live attenuated measles vaccine virus. We reviewed 773 articles for genotypic confirmation of a vaccine virus transmitted from a recently vaccinated individual to a susceptible close contact. No evidence of human-to-human transmission of the measles vaccine virus has been reported amongst the thousands of clinical samples genotyped during outbreaks or endemic transmission and individual case studies worldwide.

1. Introduction

Mass measles vaccination campaigns prevented an estimated 17.1 million deaths worldwide between 2000 and 2014 [1]. Strategically targeted vaccination has interrupted endemic measles transmission in many areas of the world, including the entire Western Hemisphere by 2002 [2,3]. In other regions, religion-based objections and concern about side effects have decreased vaccination coverage below that required for herd immunity with resulting resurgence of disease [4,5]. In nations, where elimination status has been achieved and retained, outbreaks now associated with imported measles have been observed less frequently and in lower numbers than during previous endemic transmission [2], making it feasible to examine individual cases of disease and their transmission pathways. Published clinical manifestations in individuals and genotyping of clinical samples during outbreaks have provided an opportunity to search for evidence for human-to-human transmission of the measles live attenuated vaccine virus.

The live attenuated vaccine virus superseded an inactivated form of the vaccine, which proved ineffective in generating long-term seroconversion and could prime for atypical measles when recipients were exposed to wild-type measles [6–8]. Pre-licensure clinical studies on the prototypic live attenuated Edmonston strain in small cohorts of less than a hundred children concluded the vaccine triggered an adequate immune response and there was no spread to unvaccinated close contacts [9]. The lack of respiratory symptoms reported in vaccinated children in the early 1960s and absence of detection of viral shedding in all but one case [10,11] have since been observed in multiple clinical examinations of vaccinees. Since these early studies, measles vaccine has undergone change including modification of attenuation protocols for vaccine manufacture, the introduction of vaccines from new strains, and the widespread use of trivalent measles, mumps, and rubella vaccines [12]. Hundreds of millions of measles vaccines have been administered globally, with approximately 205 million children vaccinated in 34 countries in 2013 alone [13], providing a large, vaccinated sample for a more accurate interpretation of vaccine performance and effects.

Most measles vaccines currently produced are derived from the Edmonston wild-type strain that circulated in the United States at the time the first vaccine was developed; with additional locally derived vaccines from wild-type isolates in Japan, Russia, and China

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[14]. All vaccines are attenuated by multiple passages predominantly through avian cell lines [12]. Although the functional and genetic changes to the vaccine virus resulting from attenuation have been studied [15], the molecular mechanism of attenuation has not yet been elucidated [16] making it difficult to propose a theoretical model in support for or against transmission between humans.

The 24 measles genotypes [17] are classified into eight clades (A–H) [18] with the remaining eight circulating genotypes detected by global surveillance in 2014 mapped to geographically distinct boundaries [19]. All vaccine viruses are genotype A, likely the predominant genotype circulating at the time the original vaccines were developed [20]. As the measles virus is monotypic, the antibodies generated in response to infection recognize conserved viral epitopes across all genotypes. As such, serological testing for IgM and IgG antibodies only serves to confirm an acute immune response or seroconversion respectively to measles, and is unable to distinguish between a vaccine virus and natural infection. Elucidation of the virus RNA sequence following reverse transcription-polymerase chain reaction (RT-PCR) from a clinical specimen or viral isolate in cell culture, is the only method enabling this distinction to be made [21–23]. For genotyping, the World Health Organization recommends as a minimum to amplify the 450-nucleotide sequence of the carboxyl terminal of the N gene that encodes the nucleoprotein, one of the regions of greatest diversity [24]. Identification is strengthened by amplification of the hemagglutinin and phosphoprotein genes, and an untranslated region between the matrix and fusion genes; or ultimately whole genome sequencing [25,26]. Fortuitously, all wild-type and vaccine sequences can be amplified using the same primer set [27].

Live attenuated vaccines are designed to protect against disease and not to acquire a disease-like capacity for transmission between humans. Persistent human-to-human transmission of the live attenuated oral polio vaccine was only observed once the goal of global polio elimination approached [28] and had likely been masked by the preceding prevalence of circulating wild-type disease. In a similar context for measles, low case numbers in nations with interrupted endemic transmission combined with widespread use of highly sensitive molecular genotyping tools, presents an opportunity to observe vaccine virus transmission should it exist. As such, we sought to identify any available data on the human-to-human transmission of vaccine type measles virus by a systematic review of the literature.

2. Materials and methods

A systematic literature search was performed by two reviewers independently (KG and RH). The electronic bibliographic databases PubMed, Embase, CINAHL, Scopus, and Web of Science were initially searched from January 1985 to align with the invention of PCR in 1985 and publication in 1986 [29], until March 2016. Communication of PCR methodology provided the earliest opportunity for investigators to have developed this technology to amplify measles virus strains and to laboratory confirm a vaccine genotype. To allow for the development and adoption of RT-PCR for routine measles virus RNA detection, any investigations of human-to-human transmission of the measles live attenuated vaccine virus unconfirmed by RT-PCR then genotyping within a ten-year period, were noted for discussion. An additional search was performed on articles from January 1963 or the date of inception of the search database if later, to December 1984 to identify investigations of human-to-human transmission unconfirmed by RT-PCR then genotyping. All publication types from peer-reviewed journals were included and only English language articles, or articles for which an English language translation was provided, were reviewed. A flow diagram of the screening process is shown in Fig. 1.

2.1. Literature search

Search terms used for each database are listed in Table 1. Terms were restricted to the title and abstract fields, MeSH or major headings except for Web of Science where an abstract search was not available. A public health librarian oversaw the selection of search terms. Duplicates were removed from the search results. Articles were reviewed against inclusion and exclusion criteria. Where an outbreak investigation, cluster or individual case was described, the articles were reviewed for any details of laboratory diagnostic results.

2.2. Inclusion and exclusion criteria

The main inclusion criterion was a laboratory confirmed vaccine virus genotype A isolated from a clinical sample attributed to transmission from a recently vaccinated close contact. The recipient of vaccine virus transmission could be asymptomatic or exhibit any of the clinical signs for a wild-type infection including a maculopapular rash, fever, corzya, conjunctivitis, or cough [30]; and symptoms could range from mild to severe. For studies published in 1985 or later a laboratory method describing viral RNA isolation and RT-PCR amplification then sequencing for the molecular genotype targeting the nucleoprotein N gene needed to be present. All wild-type measles virus genotypes elucidated following RT-PCR were excluded. Virus isolation alone or serological testing for measles-specific antibodies was excluded as neither differentiate a wild-type from a vaccine virus.

The recipient of vaccine virus transmission could be unvaccinated or previously vaccinated. A vaccinated individual could retain susceptibility to vaccine virus transmission if vaccine failure has occurred. Where the recipient had been vaccinated, there must be evidence that the detected vaccine virus was due to transmission and not their own vaccination, thereby eliminating the possibility of subclinical persistence of the vaccine virus or triggered replication of a dormant vaccine virus [31].

Evidence of close contact between a susceptible individual who has met the aforementioned inclusion criteria and a vaccinee who had been vaccinated within the preceding 2 months was required for inclusion. The 2-month window allowed for a maximum incubation period determined for a wild-type virus of up to 21 days [32] in addition to the virus transmission period. The wild-type virus can be transmitted from 4 days prior to 4 days after a rash appears, with rash onset 3–5 days after the first symptoms [33,34]. Therefore, at an extreme, the vaccinee may be able to transmit the vaccine virus up to 1 month after vaccination and a recipient of vaccine virus transmission could potentially begin to shed detectable vaccine virus up to 21 days later. Exposure of the susceptible individual could be close or direct contact with the vaccinee or to vaccinee secretions within 2 h of deposition [34].

No other criteria were defined for the vaccinee, such that no limits were placed on the selection of vaccine strain or administration schedule. All age groups of vaccinee and recipient were included. Having an immunocompromised state was not an exclusion criterion. Animal studies of vaccine virus transmission were excluded, as was *in vitro* research.

3. Results

A search of the five databases from January 1963 to March 2016 yielded 1732 articles from which 920 duplicate articles were removed. The number of resultant articles and the screening process is detailed in Fig. 1. An initial review of 773 articles from January 1985 onwards, representing the PCR era was assessed against the exclusion and inclusion criteria and eventually all

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