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SPECIAL ARTICLE

Oncolytic Measles Virotherapy and Opposition to Measles Vaccination

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Abstract

Recent measles epidemics in US and European cities where vaccination coverage has declined are providing a harsh reminder for the need to maintain protective levels of immunity across the entire population. Vaccine uptake rates have been declining in large part because of public misinformation regarding a possible association between measles vaccination and autism for which there is no scientific basis. The purpose of this article is to address a new misinformed antivaccination argument—that measles immunity is undesirable because measles virus is protective against cancer. Having worked for many years to develop engineered measles viruses as anticancer therapies, we have concluded (1) that measles is not protective against cancer and (2) that its potential utility as a cancer therapy will be enhanced, not diminished, by prior vaccination.

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For the past 20 years, the authors of this minireview and position statement have been developing engineered versions of measles virus as potential cancer therapies. These viruses have been shown to infect and kill cancer cells and to boost the immune response against the tumor. Unfortunately, our work is now being inappropriately and incorrectly cited by antivaccine campaigners to argue against measles vaccination.

THE QUESTION THAT PROMPTED THIS REVIEW

Recently, one of us received an email message from an exasperated teacher with the subject line "please, please make a statement about MMR (measles, mumps, rubella) vaccine." The message read as follows:

"I'm a teacher and your supportive opinion would go a lot further than all the numbers I can throw at parents. They see your work and make some judgement about measles being protective against cancer, therefore do not vaccinate their kids. Please answer. Do you advise families [to] immunize their children on schedule?"

THE ANSWER

The answer is an unequivocal YES, we do very strongly advise families to immunize their children on schedule. Measles is a serious infection capable of killing infected children. It caused 110,000 deaths worldwide in 2017.[1,2] Vaccination protects against measles and has been administered to over a billion people with an exceptional safety record. There is no evidence that measles infection

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can protect against cancer. Our studies using engineered measles viruses to treat cancer have found the best outcomes in people who have been vaccinated, and our current approaches are fully geared to this group of patients with cancer.

We are dismayed to learn that our work is being cited in opposition to MMR (measles, mumps, and rubella) vaccination and are therefore taking this opportunity to review the key pertinent facts about measles, measles vaccination, and measles as an experimental cancer therapy that support this position.

THE FACTS ABOUT MEASLES

Measles spreads in respiratory droplets and is the most transmissible virus known ("coughs and sneezes spread diseases").[3,4] The R0 (numbers of people in a susceptible population that will be infected by a single person with measles) is 15 to 20, much higher than the R0 of Ebola (1.5-2.5) or influenza (1.4-4).[5,6] After an incubation period of 9 to 11 days, the virus causes a severe head cold (conjunctivitis, swollen eyelids, photophobia, hacking cough, and nasal discharge) with associated fever, irritability, and general malaise that lasts 3 to 4 days, then gives way to a blotchy maculopapular rash that starts on the forehead, spreads down over the face, neck, and trunk to the feet, and lasts around 6 days.

Most children infected with the virus recover completely and develop lifelong immunity to reinfection. However, recovery is not guaranteed, and the infection can lead to several serious complications that are collectively responsible for the high mortality and long-term morbidity of measles.[7,8]

If the virus spreads more extensively in the body, it can cause bronchitis, bronchiolitis, viral pneumonia, corneal ulceration and blindness, myocarditis, hepatitis, and encephalomyelitis. Also, and not widely appreciated, measles in pregnancy can result in devastating loss. In one study of 58 pregnant women with active measles infection, 15 women experienced pneumonia, 13 had premature deliveries, and 5 had spontaneous abortions.[9,10]

Aside from causing damage to infected tissues, measles is powerfully immunosuppressive due to direct lymphocyte infection/killing as well as inhibiting the proliferation of uninfected lymphocytes.[4,11,12] Secondary bacterial pneumonia and bacterial otitis media are therefore frequently encountered during measles. Immunosuppression may persist for weeks after measles resolution, as evidenced by impairment of the delayed type hypersensitivity reaction to intradermal tuberculin, and patients are therefore at substantially increased risk for tuberculosis reactivation and other opportunistic infections during this time.[13] One to three in 1000 children contracting measles will have development of encephalitis concurrent with measles infection,[14] of whom 10% to 15% will die and a further 25% will have long-term neurologic damage.[15] Additional postinfectious complications include a progressive fatal encephalitis with onset 1 to 6 months postinfection in 1 in 1000 children[15] compared with 1 to 2 in 1 million following live virus vaccination,[16] and 1 in 25,000 children with measles will have development of subacute sclerosing panencephalitis with typical onset many years later.[14] In the United States, this figure has been reported to be as high as 1 in 1367 for children younger than 5 years old.[17]

Because of differences in the availability of supportive care and risk of exposure to serious opportunistic pathogens, overall measles mortality varies country to country from 0.1% to 3.0%. In 2017, 110,000 people died from measles, mostly children under age 5 years.[1] However, even the lower of these mortality numbers is frightening when caring for an infected infant and fully justifies the international effort to eradicate the disease.

Before the availability of measles vaccination, epidemics in large population centers occurred every 2 to 3 years, and 95% of children were immune by age 15 years. New epidemics therefore almost entirely impacted younger children. This was fortunate because measles in adults is more severe than measles in children.

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THE FACTS ABOUT MEASLES VACCINATION

The goal of vaccination is to induce protective levels of circulating antimeasles antibodies. This is achieved through subcutaneous injection of a small dose of a replication-competent strain of measles virus attenuated and rendered nonpathogenic by years of tissue culture passage and adaptation on a variety of cell substrates.[5]

The strain of measles virus most widely used for vaccination was originally isolated from the throat of an 11-year-old boy named David Edmonston in 1954.[18,19] In the nearly 70 years since Edmonston (Edm)—lineage viruses were first used for vaccination, there has never emerged a wild-type measles virus that can evade the neutralizing anti-Edm antibody response. Early Edm vaccines were less stringently attenuated than those currently in use and were prone to causing a mild measleslike illness (reactogenic). Newer vaccine strains are extremely well tolerated, causing only minimal and short-lived adverse effects in vaccines.[6]

Given that autism is often first manifested around the time of measles vaccination, reports of autism arising shortly after the first exposure to a measles vaccine are inevitable. However, detailed statistical analysis of the temporal relationships of vaccination to autism onset provides no support for a causal connection, nor is there a plausible mechanistic basis to even suspect a connection.[20-23]

The best way to protect a population from measles virus is to maintain immunity levels greater than 95% by vaccinating as many children as possible as soon as they are old enough to respond to the vaccine.[24,25] If vaccine coverage drops below a critical threshold level, the number of susceptible children in a population can rapidly increase to the point at which a measles epidemic can easily be sustained, whereupon most of those individuals not vaccinated will likely succumb to measles infection and population immunity will temporarily be restored to protective levels.

In the face of an advancing epidemic, nonimmune individuals can be speedily protected, either by administering pooled human gamma globulin within 6 days of virus exposure or by vaccination any time before or up to 3 days after virus exposure.[26] However, the logistics of "last-minute" vaccination during a rapidly spreading epidemic are problematic.

With high enough global vaccine coverage, it should in theory be possible to eradicate measles, and the World Health Organization is aggressively pursuing this goal.[5] However, there are significant barriers to achieving the levels of vaccine coverage required for global eradication that will need to be addressed if this dream is ever to be realized.

The first major barrier has to do with the timing of measles vaccination. Newborns are generally protected from measles by antibodies that they acquire from their mothers in utero.[27] Unfortunately, in addition to being resistant to measles infection, the babies of measles-immune mothers are also resistant to measles vaccination because their transplacentally acquired antibodies neutralize the vaccine. For this reason, vaccination is not initiated until 12 to 15 months of age in countries with low measles incidence vs 9 to 12 months of age in countries with higher incidence.[28]

These timelines create a "window of vulnerability" for children younger than 9 to 12 months once they have lost the protection of their maternally acquired antibodies, which disappear from the bloodstream with a half-life of only 1 month. For this reason, one of the major goals of measles vaccine research is to develop a vaccine that will be effective even in the presence of maternally acquired antimeasles antibodies and that can therefore be effectively administered at a younger age.[27,29,30] In this regard, we have recently engineered the surface proteins of the Edm vaccine strain to create a derivative virus that is not only effective in the presence of antibodies from vaccinated mothers but also retains the ability to stimulate the production of antibodies capable of neutralizing wild-type measles viruses.[31]

The second major barrier to measles eradication is simply getting people to vaccinate their children. This can be particularly difficult

in areas of conflict (eg, war zones) where the cost and logistics of supplying the vaccine can be highly problematic.[32] Perhaps even more challenging than war zone logistics, however, is the recent epidemic of unfounded and irrational anxieties regarding vaccine-induced autism, which is driving an ever-increasing number of parents to refuse permission for their infants to be vaccinated.[33,34]

And now, adding insult to injury, the additional argument of measles infection being "good for cancer" appears to be gaining traction.

THE FACTS ABOUT MEASLES VIROTHERAPY

Experiments of nature, such as the spontaneous regression of a large retro-orbital Burkitt lymphoma coincident with measles, point to the possibility of using measles as an anticancer drug.[35] However, it is important to emphasize there is no evidence to suggest that natural measles infection can protect against the later development of cancer.

Regarding the development of measles as an anticancer drug, the naturally occurring (wild-type) virus is a dangerous pathogen, not suitable for use as a cancer therapy. We and others therefore decided to determine whether attenuated measles strains belonging to the Edm vaccine lineage had anticancer potential, and the result of these endeavors is now an extensive literature documenting that this is indeed the case.[36,37]

Attenuated Edm-lineage measles viruses are selectively destructive to cultured human cancer cells of many different tissue origins and to human tumor xenografts grown in immunodeficient mice.[38] Various "therapeutic" genes have been added to the measles genome to further enhance its "druggability" and to increase its potency as an anticancer therapy. Moreover, technologies have been developed that allow the exquisite targeting of measles virus tropism so that it can now be engineered for highly specific infection and killing of only unwanted cancer cells.[39,40] At least 3 different measles virus constructs have been administered to date to more than 150 patients with cancer in clinical trials, and the results from those studies have been highly encouraging.[36,37,41-44]

In one study at Mayo Clinic, a 49-year-old woman with multiple myeloma that had become refractory to all available therapies (including 2 stem cell transplants) had a remarkable response to a single intravenous infusion of measles virus.[36] After a short-lived febrile reaction to the virus infusion, all 5 of her rapidly growing plasma cell tumors resolved completely and her bone marrow was completely free of myelomatous plasma cells. She did have a focal disease recurrence 9 months after measles virus infusion and again at 2 years posttreatment, but both of these relapses responded briskly to local radiation therapy and her disease remains in complete remission today, $5\frac{1}{2}$ years later, with no additional myeloma drug therapy.

Although several additional patients with cancer have responded favorably to single-agent measles virus therapy since that time, we have not yet seen a comparable durable complete remission. Careful analysis of the extensive correlative data sets amassed on this best-responding patient revealed that her tumor carried a very high mutational burden, she had a high baseline frequency of measles-reactive and tumor-reactive T cells, and, despite a history of recent measles vaccination (after her first stem cell transplant), she had virtually undetectable circulating antimeasles antibodies (S.J.R., N.P., unpublished data, 2019).

All of these parameters are now believed to have acted in concert to shape the favorable response to measles therapy in this patient. The absence of antimeasles antibodies allowed the virus to access sites of tumor growth via the bloodstream and to mediate inflammatory killing of myeloma cells in situ. The abundant antimeasles T cells were rapidly recruited to infected tumors where they further boosted the killing of measles-infected cells, thereby accelerating the recruitment of a second wave of T cells specifically recognizing a range of myeloma-specific tumor antigens and therefore capable of killing residual uninfected myeloma tumor cells.

Thus, our current perspective is that the optimal scenario for effective measles virotherapy is that the patient should, at the time of treatment, have abundant antimeasles T cells but no antimeasles antibodies. Provided the patient has previously received the measles vaccine, this ideal scenario can be achieved in the following ways: (1) by transiently depleting antimeasles antibodies pretherapy, (2) by using measles-infected cell carriers to deliver the virus, thereby evading antimeasles antibodies,[45,46] and (3) by engineering an oncolytic measles virus that is no longer recognized by antimeasles antibodies.[47,48]

All 3 of these scenarios are actively pursued at Mayo Clinic. Most advanced is the cell carrier strategy, which is being evaluated in patients with ovarian cancer using fat-derived autologous mesenchymal stem cells that are infected with measles virus and administered immediately into the peritoneal cavity[45,46] (ClinicalTrials.gov Identifier: NCT02068794). In addition to this approach, a third-generation oncolytic measles virus, resistant to antimeasles antibodies, will shortly be advanced into the translational pipeline (S.J.R., M.M.-A., unpublished data, 2019).

CONCLUSION

Measles is a very serious, highly transmissible, and potentially deadly viral infection that despite intensive efforts to achieve global vaccination coverage was still responsible for over 100,000 deaths in 2017. Recent epidemics in US and European cities where vaccination coverage is low provide a harsh reminder for the need to maintain protective levels of immunity across the entire population. Newer vaccines are being developed so that infants can be vaccinated before they lose the protection afforded by antibodies acquired transplacentally. Measles virotherapy should not be used as an argument in opposition to measles vaccination because the most promising approaches currently being developed are designed to give superior outcomes in vaccinated vs unvaccinated individuals.

Abbreviations and Acronyms: **Edm** = Edmonston

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