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Measles virus

A pathogen, vaccine, and a vector

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Abbreviations: MV, measles virus; rMV, recombinant measles virus, SSPE, subacute sclerosing panencephalitis; CSF, cerebro-spinal fluid; SLAM, signaling lymphocyte activation molecule; HIV, human immunodeficiency virus; HPV, human papilloma virus; WNV, west nile virus

Measles was an inevitable infection during the human development with substantial degree of morbidity and mortality. The severity of measles virus (MV) infection was largely contained by the development of a live attenuated vaccine that was introduced into the vaccination programs. However, all efforts to eradicate the disease failed and continued to annually result in significant deaths. The development of molecular biology techniques allowed the rescue of MV from cDNA that enabled important insights into a variety of aspects of the biology of the virus and its pathogenesis. Subsequently these technologies facilitated the development of novel vaccine candidates that induce immunity against measles and other pathogens. Based on the promising prospective, the use of MV as a recombinant vaccine and a therapeutic vector is addressed.

Introduction

Measles, also known as morbilli, is an infection of the respiratory system, immune system and skin caused by measles virus (MV), a paramyxovirus of the genus *Morbillivirus*. Measles is an exceptionally contageous viral infection with a substantial degree of morbidity and significant mortality.[1] Before an effective vaccine became available, measles was an inevitable step in human development. In fact the first scientific description of measles and its distinction from smallpox and chickenpox is credited to the Persian physician Rhazes (860–932), "*The Book of Smallpox and Measles*".[2] The symptoms usually develop 7–14 d after exposure to the virus. The initial symptoms usually include a high fever (often >40 °C), Koplik spots (spots in the mouth that usually appear 2–3 d prior to the rash and last 3–5 d), malaise, loss of appetite, red eyes, runny nose, and sometimes cough.[3] A culmination of generalized systemic infection occurs with the appearance of typical maculopapular, erythematous rash that covers much of the body; after which the recovery progresses, provided that there are no other infections or complications.[4]

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Pathogenesis of measles virus

Since MV is highly contagious, 90% of people not immune against the virus but sharing living space with an infected person will catch it. The virus spreads by respiration either directly or through aerosol.[5] The virus enters the host through the upper respiratory passages and infects the respiratory epithelium and/or the circulating immune cells located at that site. The virus infects the host by binding specifically to its receptors: SLAM (signaling lymphocyte activation molecule) that is expressed on immune cells, the CD46 (membrane cofactor protein) that is expressed on epithelial cells, and a third putative receptor that is shown to allow MV infection with the absence of the above receptors.[6-8] This type of receptor mediated entry confined the tropism of MV to humans; although nonhuman primates and some rodents are permissive to MV, no other animal reservoirs are known to exist.[9-11] After an exposure to MV an asymptomatic incubation period occurs nine to 12 days. The period of infectivity to appearance of symptoms has not been definitively established, however the classical or "acute measles" develops after an incubation period of approximately 10 days. The infected child tends to develop a mild respiratory illness, easily confused with common cold. As the severity of the symptoms increase typical signs of measles (conjuctivitis, coryza, cough and fever followed by rash) appear.[1,3,12]

Acute complications

MV infection affects multiple organ systems and complications are most common in the first 4–6 wk after an acute phase and upon the immune functions are disturbed. Although symptoms are relatively common, the severity ranges from mild and less serious such as diarrhea to more serious such as pneumonia (either viral pneumonia or secondary bacterial pneumonia), laryngotracheobronchitis, otitis media, corneal ulceration (leading to corneal scarring), stomatitis and encephalitis. Complications are usually more severe in adults who catch the virus, in malnourished and immune compromised individuals.

Complications with pregnancy

Measles remains a rare event in pregnancy in developing countries since most women of child-bearing age acquired measles at a young age.[13] However, in industrialized countries the

age distribution of measles cases is changed by immunization, resulting in measles infection in young adults. Thus, infection of MV-seronegative women would particularly cause serious complications including pneumonitis, hepatitis, premature labor, fetal loss and an increased risk of maternal death.

Delayed complications

Later or delayed complications include a prolonged/increased susceptibility to other infections that occur mainly with immune compromised individuals.[14,15]

Subacute sclerosing panencephalitis (SSPE) is another late complication of MV that leads to death. The mechanism of infection and its development remains ambiguous. However, MV is implicated in the development of the neurological diseases SSPE.[16,17] SSPE can be present many years after the acute disease. It is characterized by an insidious onset of a progressive cerebral dysfunction occurring over a course of months, and sometimes more due to slow progressive deterioration of parts of the nervous system. The initial symptoms can involve the alteration in personality and deteriorating performance with periods of remissions. The clinical diagnosis is confirmed by the detection of serum measles antibodies in the CSF. The neuropathology is accompanied by neural demyelination, and lesions involve the cerebral cortex, hippocampus, cerebellar cortex, basal ganglia, brain stem and spinal cord.[16-18] Although MV antigens were detectable within the neurons and glial cells, the virus was defective in a variety of ways and could not be cultured or isolated directly from the brain tissues; it has been rescued by fusing the explants with indicator cells that allowed transmission of infection.[19] The recovered MV contained hypermutations within the ORFs of M, F, and H (see below). Only lately, the mode of MV transmission in neurons was shown retrograde to synapsis in Hippocampal slice cultures.[20]

Fatality rates

The death rate in the 1920s was around 30% of all infected individuals whereas now, with improved hospitalization and healthcare systems, became less than 0.5% in developed countries. In populations with high levels of malnutrition and a lack of adequate healthcare, mortality remains as high as 10%. In cases of serious complications, the rate may rise to 20–30%.[21] Increased immunization has led to a 60–75% drop in measles deaths which made up 25% of the decline in mortality in children under five.[22] Although the mortality rate as a consequence of measles is declining, many risk factors remain unsolved:

Risk factors for MV infection

(1) Children with immunodeficiency due to HIV or AIDS, leukemia, or malnourished regardless of immunization status.[14,15,23] (2) Travel to areas where measles is endemic or contact with travelers to endemic areas. (3) Infants who lose passive antibody before the age of routine immunization.[3,24]

Measles Vaccine

MV vaccines were prepared from live wild type strains that have been cultured under conditions that caused them to lose virulence without losing their ability to induce immunity. MV was isolated in tissue culture from the blood samples and throat swabs taken from a student (D Edmonston) suffering from MV infection.[25] The ability to passage the virus in tissue culture led to the development of the first measles vaccine in 1963.[26,27] Both live and killed vaccines were initially developed. The inactivated vaccine provided only short-term protection and induced poor T cell responses and antibody that did not undergo affinity maturation.[28] The response to this vaccine caused an atypical measles, a more severe form of measles,[29] and was withdrawn.[30] The live attenuated vaccine Edmonston strain was highly reactogenic, thus gamma globlulin was often administered simultaneously with this vaccine.[28] By the mid 60's new strains of MV vaccines were developed by further passaging of the Edmonston vaccines in cell cultures (chicken embryos, chicken embryo fibroblasts, sheep kidney, dog kidney and human diploid cells). This method allowed the generation of the following commercial vaccines: the Edmonston Zagreb, Schwarz, AIK-C, Moraten, Attenuvax, and Rubeovax. Separate isolates, Leningrad 16 and CAM-70, were also passaged in the same manner to generate a safer MV vaccine.[31,32] These attenuated vaccines were less reactogenic and were more suitable for use in vaccination campaigns without concomitant administration of gamma globulin.[33]

Vaccination coverage

In developed countries, children are immunized against measles by the age of 18 mo, generally as part of the MMR vaccine (measles, mumps, and rubella). The vaccination is generally given at this age to avoid the interaction of the vaccine with maternal anti MV antibodies that may prevent the vaccine viruses from being effective.[3] A second dose is usually given to children between the ages of four and five, to increase rates of immunity. Vaccination rates have been high enough to make measles relatively uncommon disease. The most common adverse reactions to vaccination are fever and pain at the injection site. Life-threatening adverse reactions occur in less than one per million vaccinations (<0.0001%).[34]

In developing countries, where measles is highly endemic, WHO recommends two doses of vaccine be given at six and nine months of age. The vaccine should be given whether the child is HIV-infected or not.[35,36] The vaccine is less effective in HIV-infected infants than in the general population, but early treatment with antiretroviral drugs can increase its effectiveness.

Under the Global Vaccine Action Plan, measles and rubella are targeted for elimination by WHO by 2020, however, the persistence of the disease could be a stumbling block to global eradication. It has proven difficult to vaccinate a sufficient number of children in Europe and world-wide to eradicate the disease, because of opposition on philosophical or religious grounds, or fears of side-effects, or because some minority groups are hard to reach, or simply because parents forget to have their children vaccinated. In addition, vaccination is not mandatory in some countries in Europe, in contrast to the United States and many Latin American countries, where children must be vaccinated before they enter school.[37]

Impact of vaccination

Vaccination against MV has had a major impact on the epidemiology of measles. Before the vaccine became available theoretically

all children contracted measles.[38] An estimated 130 million cases and around 7 million deaths occurred globally each year.[3] The concerted activities of Governments, agencies and the Expanded Program on Immunization (EPI) have resulted in dramatic increase in coverage of vaccination. Worldwide, the fatality rate has been significantly reduced by a vaccination campaign led by partners in the Measles Initiative: the American Red Cross, the United States Centers for Disease Control and Prevention (CDC), the United Nations Foundation, UNICEF and the WHO. Globally, measles fell significantly from an estimated 873 000 deaths in 1999 to 345 000 in 2005 and to 56 000 in 2014 (**Table 1**).[39]

Administration of measles vaccines

Measles vaccines are usually administered subcutaneous of the freeze-dried vaccine reconstituted in saline solution or sterile/distilled water. The reconstituted vaccine is administered in 0.5 mL dose containing not less than 1000 TCID50 (tissue culture infectious doses) of live measles virus. Administration of the vaccine by an alternative route (Aerosol) was also practiced and has given equivalent seroconversion rates to the subcutaneous route in most studies.[40] Separate studies using nebulizers on schoolchildren have shown superiority of aerosol application to subcutaneous route, especially in pre-immune children.[41-43]

Immunogenicity of measles vaccine

The vaccine is highly immunogenic when it is given in the correct dose to children of appropriate age. The fact that measles vaccines are live attenuated, they have the ability to infect and replicate in the host without causing symptoms of the wild type strain. This allows MV vaccine to efficiently interact with various arms of the immune system and induce long-lived immunity against the cognate wild-type strain. Several studies reported that immunization can induce protection up to 20 y,[44,45] and that even with the fall of the antibody levels, re-exposure to the wild type strain stimulates a secondary response in which IgG levels rise rapidly and peak approximately 10–12 d post exposure.[46] In the majority of vaccinated persons re-infection with the wild-type will only cause subclinical boost of antibody levels. Cases of clinical measles have been documented in persons who had secondary vaccine failure.[47]

Development of techniques that allow the rescue of MV from cDNA

The twentieth century saw the introduction of several successful vaccines, including those against Diphtheria, Measles, Mumps, Rubella, Influenza, Hepatitis B, and yellow fever that saved millions of lives worldwide in addition to the eradication of smallpox. Due to the excellent safety record of MV live vaccines they were employed in many labs to understand the molecular mechanisms of paramyxovirus infection. However, the research in this field was lagging due to the lack of essential tools to understand, attenuation, intracellular transport and assembly as well as pathogenesis. The development of reverse genetics technologies to allow the rescue of non-segmented negative strand RNA viruses from cDNA[48] enabled: (1) insights on the genomic modification of a variety of MV isolates and the biology of these viruses; (2) insertion of marker gene sequences to allow localization of virus replication and infection; (3) develop multivalent recombinant vaccines against measles and other pathogens and, (4) engineer candidate oncolytic viruses against cancer.

Insights on the genomic modification of MV and its biology

One of the driving forces behind the reverse genetics of Mononegavirales was to gain better insight into the biology of this viral order. In fact site specific mutations, ORF elimination or modification within the MV genome became possible to answer the lagging questions. The role of the long untranslated region (UTR) of the Fusion (F) or Matrix (M) genes on virus replication and pathogenesis were studied by genetic manipulation of the full-length MV genome. A large deletion of 504 nucleotides of the 5′ UTR of the F gene did not show any propagation deficit in cell culture. However, in human thymus/liver implants engrafted to SCID mice, this mutant replicated slower and the titers were 10-fold lower than the parental strain.[49] other studies, using the same technology, found that the 3′UTR of the M gene as well as the 5′UTR of the F gene, have a cross-regulatory function on the magnitude of F and M expression, thus inhibiting/compromising MV replication and reducing its pathogenesis.[50]

Table 1. Reported measles cases according to WHO statistics

WHO-region	1980	1990	2000	2005	2014
African region	1 240 993	481 204	520 102	316 224	12 125
Region of the Americas	257 790	218 579	1755	19	3100
Eastern Mediterranean	341 624	59 058	38 592	15 069	2214
European Region	851 849	234 827	37 421	37 332	2430
South-East Asia	199 535	224 925	61 975	83 627	1540
Western Pacific	1 319 640	155 490	176 493	128 016	34 310
Worldwide	4 211 431	1 374 083	836 338	580 287	55 719

Genetically engineered wt-MV mutants devoid of the small proteins V and C (MV-V$^-$ and MV-C$^-$) replicated less extensively in macaques because they were restricted by interferon and inflammatory responses.[51] Finally, the function of the M protein was addressed by either elimination of the ORF or by replacement of this ORF by that of SSPE mutant. It was found that M protein regulates virus-envelope proteins sorting and budding in polarized epithelial cells[52] and the other mutant replicated efficiently in primary brain cells as well as the brains of transgenic mice susceptible to MV infection.[53]

Insertion of marker gene sequences to allow virus localization

Insertion of reading frames encoding various marker proteins is useful for monitoring the pathway of MV spread and replication in cells and in the organs of infected animals. The green fluorescent protein (GFP) was extensively used as a marker gene to study progress of infection[54-56] and transmission of the virus through synapsis in hippocampal slice cultures.[20,57] The GFP expressed by MV proved to be most informative in studies on the bio-distribution of MV-infected cells in transgenic mice.[58]

Development of multivalent recombinant and chimeric vaccine candidates

The modification of MV genome by enrichment of its genome by additional genes and the modification of its tropism was established upon proof-of-concept to determine: (1) the capacity of MV-genome to accommodate large inserts (exceeding 6 kb) of marker genes expressed simultaneously by the same virus (GFP, LacZ, CAT);[55] and (2) to stably express large gene inserts of other pathogens, and that the recombinant MV induces quantitative immune response against itself and the cloned gene products.[59-62] Intensive research was spent on this front to generate a variety of rMVs employing clinically approved MV vaccine strains.[32,60,63] Recombinant MVs expressing single or multiple genes of HIV[61,62,64,65] in two distant MV vaccine backbones and different HIV-gene inserts, induced significant immune responses (humoral and cellular) against the vector (MV) and the inserted antigens (HIV env and gag) upon immunization of transgenic mice. Many other important rMVs were developed in these labs (Institute Pasteur and University of Zurich/Berna Biotech), inducing neutralizing antibodies (IgG) and cellular immune responses (CD8+ T cells) against SARS-CoV,[66] HPV,[67] WNV[68] and Dengue fever[69] in addition to many other experimental MV recombinants.[64]

Pre-existing immunity toward MV (more than 90% of the population is either vaccinated or naturally immunized) has been a continuous concern, especially since rMVs would target not only the infants but also adults. A recent study addressing this concern showed that the pre-existing antibody titers above 500mIU per ml of serum is inhibitory to rMV immunization and thus a higher dose to prime an immune response may be necessary.[70] In addition, an alternative route to application of rMV to circumvent pre-existing antibodies would be the aerosol route.[41-43,70]

Engineering of candidate oncolytic MVs against cancer

To specifically infect and destroy cancer cells was illusive for long time, however, methods to engineer viruses, with intrinsic cytolytic function, to specifically target cancer cells is now at reach. A revolutionary approach was done after the rescue of MV from cDNA.[48] This technology allowed genetic engineering of the MV genome "at will" to generate a mutant that is fully replicating. A primordial step toward engineering a targeted MV was to determine whether envelope swaps or modification of the attachment proteins H and/or is feasible. The swap of the viral envelope glycoproteins (F and H) by an envelope glycoprotein of a different virus (VSV-G) was practically efficient and the novel chimeric virus (MV-VSV) replicated in a variety of cells including cells lines that are not susceptible to MV, indicating a change in the tropism of MV. In addition, the chimeric virus induced protective immunity to VSV susceptible mice. A heterologous challenge of these animals with 10-fold lethal dose of VSV was not effective.[71,72] These finding opened the way toward genetic manipulation of MV envelope proteins to specifically target Cancer cells. Indeed, researchers at Mayo Clinic were able to generate various mutant-MVs that target specific cells.[73] However, before probing an engineered MV in clinical trials it was necessary to determine whether standard MV vaccine itself is safe and efficacious for use in patients with cancer and whether MV is cytolytic to cancer cells, as observed in experimental animal model.[74] A decisive clinical trial performed at the University Hospital Zürich-Switzerland that provided the proof-of-concept on using MV as an oncolytic vector.[74-76] Important development in this field was crowned with clinical trials led by Mayo Clinic-USA using genetically modified MV and showed positive impact and a promising prospective for the use of MV vector against cancer.[78-80]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Krugman S, Katz SL, Gershon AA, Wilfert C. Measles. In: Infectious diseases of Children 1985; 8th edn. Mosby, St Louis, 152-166.
2. Otri AM, Singh AD, Dua HS. Cover illustration. Abu Bakr Razi. [BMJ Group]. Br J Ophthalmol 2008; 92:1324; PMID:18815419
3. Clements CJ, Cutts FT. The epidemiology of measles: thirty years of vaccination. Curr Top Microbiol Immunol 1995; 191:13-33; PMID:7789156; http://dx.doi.org/10.1007/978-3-642-78621-1_2
4. Chen SSP, Fennelly G, Burnett M, Domachowske J, Dyne PL, Elston DM, et al. "Measles" 2014; In Steele, RW. *Medscape Reference*. WebMD. Retrieved 23 March 2014
5. Risk of infection East and Southwest Asia (Report). Occucare International. May 16, 2012; p. 6
6. Wild TF, Buckland R. Functional aspects of envelope-associated measles virus proteins. Curr Top Microbiol Immunol 1995; 191:51-64; PMID:7789162; http://dx.doi.org/10.1007/978-3-642-78621-1_4
7. Yanagi Y, Takeda M, Ohno S, Hashiguchi T. Measles virus receptors. Curr Top Microbiol Immunol 2009; 329:13-30; PMID:19198560; http://dx.doi.org/10.1007/978-3-540-70523-9_2
8. Kemper C, Atkinson JP. Measles virus and CD46. Curr Top Microbiol Immunol 2009; 329:31-57; PMID:19198561; http://dx.doi.org/10.1007/978-3-540-70523-9_3
9. Sakaguchi M, Yoshikawa Y, Yamanouchi K, Sata T, Nagashima K, Takeda K. Growth of measles virus in epithelial and lymphoid tissues of cynomolgus monkeys. Microbiol Immunol 1986; 30:1067-73; PMID:3796316; http://dx.doi.org/10.1111/j.1348-0421.1986.tb03036.x
10. Yamanouchi K, Chino F, Kobune F, Kodama H, Tsuruhara T. Growth of measles virus in the lymphoid tissues of monkeys. J Infect Dis 1973; 128:795-9; PMID:4203079; http://dx.doi.org/10.1093/infdis/128.6.795
11. Liebert UG, Finke D. Measles virus infections in rodents. Curr Top Microbiol Immunol 1995; 191:149-66; PMID:7789158; http://dx.doi.org/10.1007/978-3-642-78621-1_10
12. Baxby D. Classic Paper: Henry Koplik. The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal membrane. Rev Med Virol 1997; 7:71-4; PMID:10398471; http://dx.doi.org/10.1002/(SICI)1099-1654(199707)7:2<71::AID-RMV185>3.0.CO;2-S
13. Kanda E, Yamaguchi K, Hanaoka M, Matsui H, Sago H, Kubo T. Low titers of measles antibodies in Japanese pregnant women: a single-center study. J Obstet Gynaecol Res 2013; 39:500-3; PMID:22925573; http://dx.doi.org/10.1111/j.1447-0756.2012.01997.x
14. Breitfeld V, Hashida Y, Sherman FE, Odagiri K, Yunis EJ. Fatal measles infection in children with leukemia. Lab Invest 1973; 28:279-91; PMID:4348408
15. Gowda VK, Sukanya V, Shivananda. Acquired immunodeficiency syndrome with subacute sclerosing panencephalitis. Pediatr Neurol 2012; 47:379-81; PMID:23044024; http://dx.doi.org/10.1016/j.pediatrneurol.2012.06.020
16. Anlar B. Subacute sclerosing panencephalitis and chronic viral encephalitis. Handb Clin Neurol 2013; 112:1183-9; PMID:23622327; http://dx.doi.org/10.1016/B978-0-444-52910-7.00039-8
17. Ter Meulen V, Stephenson JR, Kreth HW. Subacute sclerosing panencephalitis. In Fraenkel-Conrat H, Wagner RR (eds) Compr Virol 1983; 18: 105-159.
18. Katz M. Clinical spectrum of measles. Curr Top Microbiol Immunol 1995; 191:1-12; PMID:7789153; http://dx.doi.org/10.1007/978-3-642-78621-1_1
19. ter Meulen V, Müller D, Käckell Y, Katz M, Meyermann R. Isolation of infectious measles virus in measles encephalitis. Lancet 1972; 2:1172-5; PMID:4117594; http://dx.doi.org/10.1016/S0140-6736(72)92595-0
20. Ehrengruber MU, Ehler E, Billeter MA, Naim HY. Measles virus spreads in rat hippocampal neurons by cell-to-cell contact and in a polarized fashion. J Virol 2002; 76:5720-8; PMID:11992000; http://dx.doi.org/10.1128/JVI.76.11.5720-5728.2002
21. Measles, World Health Organization Fact sheet N°286. Retrieved June 28, 2012; Updated February 2014
22. Millennium Development Goals. United Nations. Retrieved 18 March 2013
23. Polonsky JA, Ronsse A, Ciglenecki I, Rull M, Porten K. High levels of mortality, malnutrition, and measles, among recently-displaced Somali refugees in Dagahaley camp, Dadaab refugee camp complex, Kenya, 2011. Confl Health 2013; 7:1; PMID:23339463; http://dx.doi.org/10.1186/1752-1505-7-1
24. Diaz T, Nuñez JC, Rullan JV, Markowitz LE, Barker ND, Horan J. Risk factors associated with severe measles in Puerto Rico. Pediatr Infect Dis J 1992; 11:836-40; PMID:1408482; http://dx.doi.org/10.1097/00006454-199210000-00006
25. Enders JF, Peebles TC. Propagation in tissue cultures of cytopathogenic agents from patients with measles. Proc Soc Exp Biol Med 1954; 86:277-86; PMID:13177653; http://dx.doi.org/10.3181/00379727-86-21073
26. Enders JF. Measles virus. Historical review, isolation, and behavior in various systems. Am J Dis Child 1962; 103:282-7; PMID:13890170; http://dx.doi.org/10.1001/archpedi.1962.02080020294021
27. Katz SL, Enders JF, Holloway A. The development and evaluation of an attenuated measles virus vaccine. Am J Public Health Nations Health 1962; 52(2):5-10; PMID:14454407; http://dx.doi.org/10.2105/AJPH.52.Suppl_2.5
28. Krugman S, Giles JP, Friedman H, Stone S. Studies on immunity to measles. J Pediatr 1965; 66:471-88; PMID:14264306; http://dx.doi.org/10.1016/S0022-3476(65)80112-3
29. Karzon DT, Rush D, Winkelstein W Jr. Immunization with inactivated measles virus vaccine: effect of booster dose and response to natural challenge. Pediatrics 1965; 36:40-50; PMID:14313365
30. Centers for Disease Control Recommendations of the public health service advisory committee on immunization and practice. Measles vaccines. Morb Mortal Wkly Rep 1967; 16:269-71
31. Rima BK, Earle JA, Baczko K, Rota PA, Bellini WJ. Measles virus strain variations. Curr Top Microbiol Immunol 1995; 191:65-83; PMID:7789163; http://dx.doi.org/10.1007/978-3-642-78621-1_5
32. Zuniga A, Liniger M, Morin TN, Marty RR, Wiegand M, Ilter O, Weibel S, Billeter MA, Knuchel MC, Naim HY. Sequence and immunogenicity of a clinically approved novel measles virus vaccine vector. Hum Vaccin Immunother 2013; 9:607-13; PMID:23324616; http://dx.doi.org/10.4161/hv.23242
33. Griffin DE, Pan CH. Measles: old vaccines, new vaccines. Curr Top Microbiol Immunol 2009; 330:191-212; PMID:19203111; http://dx.doi.org/10.1007/978-3-540-70617-5_10
34. Galindo BM, Concepción D, Galindo MA, Pérez A, Saiz J. Vaccine-related adverse events in Cuban children, 1999-2008. MEDICC Rev 2012; 14:38-43; PMID:22334111
35. Helfand RF, Witte D, Fowlkes A, Garcia P, Yang C, Fudzulani R, Walls L, Bae S, Strebel P, Broadhead R, et al. Evaluation of the immune response to a 2-dose measles vaccination schedule administered at 6 and 9 months of age to HIV-infected and HIV-uninfected children in Malawi. J Infect Dis 2008; 198:1457-65; PMID:18828743; http://dx.doi.org/10.1086/592756
36. Ołdakowska A, Marczyńska M. [Measles vaccination in HIV infected children]. Med Wieku Rozwoj 2008; 12:675-80; PMID:19418943
37. Kupferschmidt K. Public health. Europe's embarrassing problem. Science 2012; 336:406-7; PMID:22539695; http://dx.doi.org/10.1126/science.336.6080.406
38. Hilleman MR. Past, present, and future of measles, mumps, and rubella virus vaccines. Pediatrics 1992; 90:149-53; PMID:1603640
39. Measles Surveillance Data after WHO, last updated 2014-3-6WHO: Global summary on measles, 2006 http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/
40. Khanum S, Uddin N, Garelick H, Mann G, Tomkins A. Comparison of Edmonston-Zagreb and Schwarz strains of measles vaccine given by aerosol or subcutaneous injection. Lancet 1987; 1:150-3; PMID:2879981; http://dx.doi.org/10.1016/S0140-6736(87)91978-7
41. Dilraj A, Sukhoo R, Cutts FT, Bennett JV. Aerosol and subcutaneous measles vaccine: measles antibody responses 6 years after re-vaccination. Vaccine 2007; 25:4170-4; PMID:17408818; http://dx.doi.org/10.1016/j.vaccine.2007.03.003
42. Bennett JV, Fernandez de Castro J, Valdespino-Gomez JL, Garcia-Garcia MdeL, Islas-Romero R, Echaniz-Aviles G, Jimenez-Corona A, Sepulveda-Amor J. Aerosolized measles and measles-rubella vaccines induce better measles antibody booster responses than injected vaccines: randomized trials in Mexican schoolchildren. Bull World Health Organ 2002; 80:806-12; PMID:12471401
43. Dilraj A, Cutts FT, de Castro JF, Wheeler JG, Brown D, Roth C, Coovadia HM, Bennett JV. Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: a randomised trial. Lancet 2000; 355:798-803; PMID:10711928; http://dx.doi.org/10.1016/S0140-6736(99)95140-1
44. Miller C. Live measles vaccine: a 21 year follow up. Br Med J (Clin Res Ed) 1987; 295:22-4; PMID:3113599; http://dx.doi.org/10.1136/bmj.295.6589.22
45. Xiang JZ, Chen ZH. Measles vaccine in the People's Republic of China. Rev Infect Dis 1983; 5:506-10; PMID:6879006; http://dx.doi.org/10.1093/clinids/5.3.506
46. Zhiang Y, Su W. Introduction to the control of measles by vaccination in the People's Republic of China. Rev Infect Dis 1983; 5:568-73; PMID:6879016; http://dx.doi.org/10.1093/clinids/5.3.568
47. Reyes MA, de Borrero MF, Roa J, Bergonzoli G, Saravia NG. Measles vaccine failure after documented seroconversion. Pediatr Infect Dis J 1987; 6:848-51; PMID:3670952; http://dx.doi.org/10.1097/00006454-198709000-00012
48. Radecke F, Spielhofer P, Schneider H, Kaelin K, Huber M, Dötsch C, Christiansen G, Billeter MA. Rescue of measles viruses from cloned DNA. EMBO J 1995; 14:5773-84; PMID:8846771
49. Valsamakis A, Schneider H, Auwaerter PG, Kaneshima H, Billeter MA, Griffin DE. Recombinant measles viruses with mutations in the C, V, or F gene have altered growth phenotypes in vivo. J Virol 1998; 72:7754-61; PMID:9733811

50. Takeda M, Ohno S, Seki F, Nakatsu Y, Tahara M, Yanagi Y. Long untranslated regions of the measles virus M and F genes control virus replication and cytopathogenicity. J Virol 2005; 79:14346-54; PMID:16254369; http://dx.doi.org/10.1128/JVI.79.22.14346-14354.2005
51. Devaux P, Hodge G, McChesney MB, Cattaneo R. Attenuation of V- or C-defective measles viruses: infection control by the inflammatory and interferon responses of rhesus monkeys. J Virol 2008; 82:5359-67; PMID:18385234; http://dx.doi.org/10.1128/JVI.00169-08
52. Naim HY, Ehler E, Billeter MA. Measles virus matrix protein specifies apical virus release and glycoprotein sorting in epithelial cells. EMBO J 2000; 19:3576-85; PMID:10899112; http://dx.doi.org/10.1093/emboj/19.14.3576
53. Patterson JB, Cornu TI, Redwine J, Dales S, Lewicki H, Holz A, Thomas D, Billeter MA, Oldstone MB. Evidence that the hypermutated M protein of a subacute sclerosing panencephalitis measles virus actively contributes to the chronic progressive CNS disease. Virology 2001; 291:215-25; PMID:11878891; http://dx.doi.org/10.1006/viro.2001.1182
54. Duprex WP, McQuaid S, Hangartner L, Billeter MA, Rima BK. Observation of measles virus cell-to-cell spread in astrocytoma cells by using a green fluorescent protein-expressing recombinant virus. J Virol 1999; 73:9568-75; PMID:10516065
55. Zuniga A, Wang Z, Liniger M, Hangartner L, Caballero M, Pavlovic J, Wild P, Viret JF, Glueck R, Billeter MA, et al. Attenuated measles virus as a vaccine vector. Vaccine 2007; 25:2974-83; PMID:17303293; http://dx.doi.org/10.1016/j.vaccine.2007.01.064
56. Duprex WP, Collins FM, Rima BK. Modulating the function of the measles virus RNA-dependent RNA polymerase by insertion of green fluorescent protein into the open reading frame. J Virol 2002; 76:7322-8; PMID:12072530; http://dx.doi.org/10.1128/JVI.76.14.7322-7328.2002
57. Ehrengruber MU, Hennou S, Büeler H, Naim HY, Déglon N, Lundstrom K. Gene transfer into neurons from hippocampal slices: comparison of recombinant Semliki Forest Virus, adenovirus, adeno-associated virus, lentivirus, and measles virus. Mol Cell Neurosci 2001; 17:855-71; PMID:11358483; http://dx.doi.org/10.1006/mcne.2001.0982
58. Peng KW, Frenzke M, Myers R, Soeffker D, Harvey M, Greiner S, Galanis E, Cattaneo R, Federspiel MJ, Russell SJ. Biodistribution of oncolytic measles virus after intraperitoneal administration into Ifnar-CD46Ge transgenic mice. Hum Gene Ther 2003; 14:1565-77; PMID:14577918; http://dx.doi.org/10.1089/104303403322495070
59. Wang Z, Hangartner L, Cornu TI, Martin LR, Zuniga A, Billeter MA, Naim HY. Recombinant measles viruses expressing heterologous antigens of mumps and simian immunodeficiency viruses. Vaccine 2001; 19:2329-36; PMID:11257357; http://dx.doi.org/10.1016/S0264-410X(00)00523-5
60. Tangy F, Naim HY. Live attenuated measles vaccine as a potential multivalent pediatric vaccination vector. Viral Immunol 2005; 18:317-26; PMID:16035943; http://dx.doi.org/10.1089/vim.2005.18.317
61. Liniger M, Zuniga A, Morin TN, Combardiere B, Marty R, Wiegand M, Ilter O, Knuchel M, Naim HY. Recombinant measles viruses expressing single or multiple antigens of human immunodeficiency virus (HIV-1) induce cellular and humoral immune responses. Vaccine 2009; 27:3299-305; PMID:19200842; http://dx.doi.org/10.1016/j.vaccine.2009.01.057
62. Liniger M, Zuniga A, Naim HY. Use of viral vectors for the development of vaccines. Expert Rev Vaccines 2007; 6:255-66; PMID:17408374; http://dx.doi.org/10.1586/14760584.6.2.255
63. Combredet C, Labrousse V, Mollet L, Lorin C, Delebecque F, Hurtrel B, McClure H, Feinberg MB, Brahic M, Tangy F. A molecularly cloned Schwarz strain of measles virus vaccine induces strong immune responses in macaques and transgenic mice. J Virol 2003; 77:11546-54; PMID:14557640; http://dx.doi.org/10.1128/JVI.77.21.11546-11554.2003
64. Zuniga A, Liniger M, Morin TN, Marty RR, Wiegand M, Ilter O, Weibel S, Billeter MA, Knuchel MC, Naim HY. Sequence and immunogenicity of a clinically approved novel measles virus vaccine vector. Hum Vaccin Immunother 2013; 9:607-1; PMID:23324616; http://dx.doi.org/10.4161/hv.23242
65. Lorin C, Mollet L, Delebecque F, Combredet C, Hurtrel B, Charneau P, Brahic M, Tangy F. A single injection of recombinant measles virus vaccines expressing human immunodeficiency virus (HIV) type 1 clade B envelope glycoproteins induces neutralizing antibodies and cellular immune responses to HIV. J Virol 2004; 78:146-57; PMID:14671096; http://dx.doi.org/10.1128/JVI.78.1.146-157.2004
66. Liniger M, Zuniga A, Tamin A, Azzouz-Morin TN, Knuchel M, Marty RR, Wiegand M, Weibel S, Kelvin D, Rota PA, et al. Induction of neutralising antibodies and cellular immune responses against SARS coronavirus by recombinant measles viruses. Vaccine 2008; 26:2164-74; PMID:18346823
67. Cantarella G, Liniger M, Zuniga A, Schiller J-T, Billeter M, Naim HY, Glueck R. Recombinant measles virus-HPV vaccine candidates for prevention of cervical carcinoma. Vaccine 2009; 27:3385-90; PMID:19200837; http://dx.doi.org/10.1016/j.vaccine.2009.01.061
68. Desprès P, Combredet C, Frenkiel MP, Lorin C, Brahic M, Tangy F. Live measles vaccine expressing the secreted form of the West Nile virus envelope glycoprotein protects against West Nile virus encephalitis. J Infect Dis 2005; 191:207-14; PMID:15609230; http://dx.doi.org/10.1086/426824
69. Brandler S, Tangy F. Recombinant vector derived from live attenuated measles virus: potential for flavivirus vaccines. Comp Immunol Microbiol Infect Dis 2008; 31:271-91; PMID:17869338; http://dx.doi.org/10.1016/j.cimid.2007.07.012
70. Knuchel M, Marty RR, Azzouz Morin TN, Ilter O, Zuniga A, Naim HY. Relevance of pre-existing immunity against recombinant measles vector. Hum Vaccin Immunother 2013; 9:599-606; PMID:23324399; http://dx.doi.org/10.4161/hv.23241
71. Spielhofer P, Bächi T, Fehr T, Christiansen G, Cattaneo R, Kaelin K, Billeter MA, Naim HY. Chimeric measles viruses with a foreign envelope. J Virol 1998; 72:2150-9; PMID:9499071
72. Fehr T, Naim HY, Bachmann MF, Ochsenbein AF, Spielhofer P, Bucher E, Hengartner H, Billeter MA, Zinkernagel RM. T-cell independent IgM and enduring protective IgG antibodies induced by chimeric measles viruses. Nat Med 1998; 4:945-8; PMID:9701248; http://dx.doi.org/10.1038/nm0898-945
73. Russell SJ, Peng KW. Measles virus for cancer therapy. Curr Top Microbiol Immunol 2009; 330:213-41; PMID:19203112; http://dx.doi.org/10.1007/978-3-540-70617-5_11
74. Künzi V, Oberholzer PA, Heinzerling L, Dummer R, Naim HY. Recombinant measles virus induces cytolysis of cutaneous T-cell lymphoma in vitro and in vivo. J Invest Dermatol 2006; 126:2525-32; PMID:16960554; http://dx.doi.org/10.1038/sj.jid.5700529
75. Heinzerling L, Künzi V, Oberholzer PA, Kündig T, Naim H, Dummer R. Oncolytic measles virus in cutaneous T-cell lymphomas mounts antitumor immune responses in vivo and targets interferon-resistant tumor cells. Blood 2005; 106:2287-94; PMID:15961518; http://dx.doi.org/10.1182/blood-2004-11-4558
76. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nat Biotechnol 2012; 30:658-70; http://dx.doi.org/10.1038/nbt.2287; PMID:22781695
77. Elsedawy NB, Russell SJ. Oncolytic vaccines. Expert Rev Vaccines 2013; 12:1155-72; http://dx.doi.org/10.1586/14760584.2013.836912; PMID:24124877
78. Russell SJ, Federspiel MJ, Peng KW, Tong C, Dingli D, Morice WG, Lowe V, O'Connor MK, Kyle RA, Leung N, et al. Remission of disseminated cancer after systemic oncolytic virotherapy. Mayo Clin Proc 2014; 89:926-33; http://dx.doi.org/10.1016/j.mayocp.2014.04.003; PMID:24835528
79. Msaouel P, Opyrchal M, Domingo Musibay E, Galanis E. Oncolytic measles virus strains as novel anticancer agents. Expert Opin Biol Ther 2013; 13:483-502; http://dx.doi.org/10.1517/14712598.2013.749851; PMID:23289598
80. Galanis E. Therapeutic potential of oncolytic measles virus: promises and challenges. Clin Pharmacol Ther 2010; 88:620-5; PMID:20881957; http://dx.doi.org/10.1038/clpt.2010.211