

Could this be measles?

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ABSTRACT

Infection with the measles virus causes an unpleasant disease with many potentially serious complications. It is predominantly a childhood illness but can affect any age. Measles is extraordinarily contagious, but immunisation with measles containing vaccine provides comprehensive protection. An international programme of universal immunisation from the mid-1980s has been very effective; measles was declared eliminated in the USA nearly two decades ago and became a rarity in other countries with high rates of vaccine uptake. Until recently, this was a forgotten disease in high-income countries, but paediatricians, emergency and primary care physicians worldwide are now encountering measles with increased frequency. Attributed to international travel and pockets of vaccine hesitancy locally, new outbreaks of measles have been recorded in many regions thought to have been free of the disease. Because it was previously so uncommon, measles presents a diagnostic challenge and an unrecognised case may cause infection to spread among communities. The present article presents a case of confirmed measles infection and discusses the epidemiology, clinical features, investigation, management and prevention of measles.

CASE

In May 2018, an 8-year-old boy presented to the children's ED with a 4-day history of fever, malaise, loose non-productive cough, vomiting and anorexia. The child was reportedly fully vaccinated and had enjoyed good health in the past. There had been no recent foreign travel, but his 18-year-old brother had recently travelled to Indonesia and had reported similar symptoms on his return.

On examination, the child was coryzal with a temperature of 39.4°C, respiratory rate 21 bpm with clear chest and oxygen saturation of 100% on room air. The heart rate was 130 bpm, and capillary return time was less than 2s. Ear and throat examinations were unremarkable, and there was no cervical lymphadenopathy.

There was vivid bilateral conjunctivitis and a maculopapular rash on the face and around the eyes. There was no generalised rash and no involvement of the extremities or mucous membranes.

Bloods were drawn for full blood count and differential, routine biochemistry, C reactive protein, Anti-streptococcal O titre (ASOT) and measles and rubella antibodies.

QUESTIONS

- How does measles present?
- What are the complications of measles?
- Where in the world is measles?

ANSWERS

How does measles present?

Measles is usually encountered during spring and early summer but may be seen at any time. The peak incidence is in March and reported cases become relatively uncommon during the second half of the year. Patients with uncertain vaccination status, including adults and children, who return from endemic countries must be considered to be at risk of measles infection. Measles can occur at any age but is most often seen in children under 5 years, and the highest mortality is in this age group. Lack of vaccination is the major risk factor for the development of the disease, other factors include immunosuppression, prematurity and lack of maternal vaccination. Measles antibodies cross the placenta in the third trimester, and premature infants prior to their first MMR vaccination have lower antibody titres than term babies.

Individuals with impaired cell-mediated immunity, including postorgan transplantation, HIV disease, lymphoma and T cell suppressive therapy, are at increased risk of atypical measles (*vide infra*) and its complications. A positive history of immunisation is not a reliable indicator of immunity in these patients, and any suspicion of measles should warrant investigation and treatment. Pregnancy is not a recognised risk factor for the development of measles, but measles infection in pregnancy is associated with severe maternal and fetal complications, including intrauterine fetal death.

The incubation period for measles is 6–21 days (median 13 days). Patients are usually asymptomatic during the incubation period. The illness begins with fever, which can rise to 40°C by day 5, malaise and anorexia. Conjunctivitis, coryza and cough develop next and may intensify for a few days just before the appearance of the rash. The exanthem is preceded by buccal mucosal blemishes known as Koplik's spots, pathognomonic when present and appearing approximately 48 hours before the rash. These are 1–3 mm white/grey elevations on an erythematous base, typically on the buccal membrane opposite the molar teeth. They generally last for 12–72 hours and tend to coalesce by the time the skin rash appears.

The rash is maculopapular and appears first on the face, typically behind the ears, and spreads caudally to include the neck, trunk and extremities. Palms and soles are usually spared. Initially blanching, the spots become non-blanching over days. Associated symptoms include high fever and cervical lymphadenopathy. In uncomplicated cases clinical improvement begins within 48 hours of the development of the rash. Spots start to fade from about 6 days after their appearance.



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Vaccine-modified measles is a less severe disease that occurs in persons with some pre-existing immunity due to prior infection or immunisation, transplacental transfer of antibodies or non-immune individuals who have received intravenous immunoglobulins for unrelated conditions. Patients with modified measles are less infective but may still present a risk to unimmunised contacts.¹ Atypical measles syndrome (AMS) is a very rare form of the disease affecting adolescents and young adults. It was first described in association with vaccines of a previous era but is still occasionally encountered. AMS is characterised by sudden onset of prolonged fever with headache, cough, abdominal pain and peripheral oedema. The rash is polymorphous and more vivid than in classic measles, and it may have a petechial element. Respiratory symptoms due to pulmonary infiltrates may be severe enough to cause respiratory failure. The chest X-ray may show bilateral pulmonary nodules and hilar lymphadenopathy. The laboratory findings include eosinophilia and raised hepatic aminotransferases. There is a rapid rise in measles IgM antibody titre between the first and tenth day of the illness. Patients with AMS are thought not to be infective to others.²

What are the complications of measles?

One or more complications occur in up to 30% of individuals infected with measles.³ Diarrhoea is the most common complication with an occurrence rate of 8%. Otitis media is seen most often in younger children. Measles infection causes immunosuppression and infected individuals are at risk of coinfection with respiratory and gastrointestinal viruses, and secondary bacterial infections, particularly with *Staphylococcus*, *Streptococcus* and *Haemophilus influenzae*.

Pneumonia complicates approximately 6% of measles infections and is the most common cause of measles-associated death. Encephalitis occurs in 1 per 1000 cases and presents as fever, headache, vomiting, neck stiffness, meningeal irritation, drowsiness, convulsions and coma. Acute disseminating encephalomyelitis (ADEM) is a postinfectious demyelinating disease of the central nervous system (CNS) and occurs in 1 in 1000 cases of measles. ADEM presents in the recovery phase within 2 weeks of the exanthem. Symptoms include fever, headache, neck stiffness, confusion, paraesthesia, sensory loss, new onset incontinence and choreoathetosis. Mortality rates for ADEM are around 10%–20%. Subacute sclerosing panencephalitis (SSPE) is a late onset lethal progressive degenerative disease of the CNS. It presents 7–10 years after initial measles infection. The pathogenesis is not well understood, but risk factors include measles infection occurring before the second birthday. Symptoms of SSPE start with mild to moderate behavioural changes, progressing to a dementia-like disorder with associated myoclonic jerks. Symptoms progress until a vegetative state is reached with eventual fatal outcome.

Where in the world is measles?

Measles is a worldwide disease; the average incidence is around 19 cases per million with significant variation by country. Worldwide, there are an estimated 100 000 deaths annually, mostly among children under 5 years of age.⁴ The greatest number of cases is reported in the Indian subcontinent where incidence rates exceed 50 per million of the population per annum.

Some high-income countries have achieved elimination status as a result of comprehensive vaccination and surveillance programmes. However, in many parts of the world, including Europe, Central and South America, Asia, the Pacific and Africa, the disease remains endemic. Consequently, outbreaks

are occurring in countries previously thought to be free of the disease.

In the USA, measles was declared eliminated in the year 2000, defined as the absence of endemic measles virus transmission for at least 12 months. Occasional outbreaks (three or more linked cases) are still reported to the Centers for Disease Control and Prevention (CDC) each year, often imported from overseas and spreading among communities with low rates of immunisation. In 2018, there were 349 cases reported to CDC, consistent with previous years. By the end of February 2019, there were 206 confirmed cases from six outbreaks, the largest of which was in the Pacific Northwest.⁵ There are only a handful of measles cases in Canada each year, and the disease presents a risk to Canadians travelling abroad, including to Europe.⁶ Measles has also been eliminated in Australia and New Zealand with import-related cases, usually from South East Asia, accounting for a few cases a year in that country.

Improved levels of vaccination in Europe led to reduced levels of infection in the first 15 years of this century, recovering from a steep decline in MMR (mumps, measles and rubella) vaccine uptake following the now discredited assertions linking the vaccine to the development of autism in 1998. ‘Vaccine hesitancy’ remains an issue, however, and has been identified as one of the major threats to global health in 2019, leading to a resurgence of the disease in high-income countries.⁷ In the UK, the incidence of measles fell from 32.2 to 10.4 confirmed cases per million of the population between 2012 and 2016. However, there was a surge in the number of reported cases among many European countries in 2017, and in that year, there were 282 cases in the UK, attributed to cases imported from overseas and reduced vaccine uptake, especially among certain disadvantaged groups. Throughout the continent in that year, there were more than 21 000 cases and 35 deaths.⁸ In the first 6 months of 2018, there were more than 41 000 cases and at least 37 deaths. Ukraine, Romania and Serbia were particularly affected by the disease and its complications, but the WHO has advised that every non-immunised person is vulnerable to the disease, no matter where they live.⁹ International travel continues to allow measles importation of measles from endemic countries to countries that have achieved elimination.

Measles is highly contagious and will spread rapidly among communities unless there is at least 95% population coverage with two doses of measles-containing vaccine (MCV). Measles immunisation coverage among children is around 85% globally. The lowest rates are in Southeast Asia (75%) and Africa (73%) and the highest are in Europe (94%). In low-income countries, 76% of children aged 12–23 months have received measles vaccination, compared with 82% in lower middle-income countries, 94% in upper middle-income countries and 93% in high-income countries.⁴ Immunisation rates in Indonesia fell substantially after some clerics condemned the vaccines because of concerns over porcine-derived components. The CDC has warned of a possible outbreak in that country and has advised travellers accordingly.¹⁰

CASE PROGRESSION

The patient’s general practitioner was contacted by telephone and advised that the child was not, in fact, fully immunised and was due his first MMR vaccine the following day. Moreover, the child’s older brother, also unimmunised, had now been diagnosed with classic measles infection during a short stay in a general medical ward at the same hospital; measles RNA and IgM were positive.

The 7-year-old child was given antipyretics and was allowed home on the advice of a consultant virologist when symptoms had settled. The diagnosis of suspected measles infection was communicated to the local health protection team.

QUESTIONS

- i. How is measles diagnosed?
- ii. How should a case of suspected measles be managed in the ED?
- iii. How contagious is measles?

ANSWERS

How is measles diagnosed?

The measles virus is morbillivirus of the paramyxovirus family with 24 described genotypes. The virus has been isolated in some non-human primates, but the natural host is human. The initial diagnosis of measles is clinical. Confirmatory tests (on saliva, mouth and throat swabs and blood samples) are not available for several days and are relevant to the health of the public. PCR testing identifies the presence of specific viral RNA in samples and is the earliest available confirmatory test, yielding results within 1–3 days. Genotyping on PCR-positive samples allows characterisation of the virus to identify clusters or imported cases and to monitor progress towards elimination during outbreaks. Where the rash develops after vaccination genotyping also allows to distinguish between wild type virus and vaccine-related antigen.

The 'three Cs' of coryza, conjunctivitis and cough are common early symptoms of measles. This triad marks the prodrome, and symptoms may become more severe as the disease progresses. The differential diagnosis depends on the stage of the disease; prodromal symptoms may be confused with any of the numerous self-limiting virus infections seen in children. The established disease may prompt consideration of Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) infection, rubella, erythema infectiosum, scarlet fever and Kawasaki disease. Autoimmune diseases and drug eruptions may also be considered, and in relevant geographic regions, Rocky Mountain spotted fever and dengue fever. A measles-like illness may be seen after a minor wound or burn in younger children with staphylococcal toxic shock syndrome.

In advanced healthcare settings, immunological tests are used to confirm the diagnosis. Saliva is the optimal sample in the first few days after the rash; IgM antibodies are positive in over 50% of samples on day 1 of the rash and in over 90% by day 3, remaining positive for up to 14 days. Saliva can be tested for antibodies IgM, IgG and measles RNA using specific enzyme immunoassays. Measles RNA can be detected in samples from onset of rash until 2 weeks after symptom onset. Testing on saliva can also distinguish between primary and recurrent infection and enables genotyping of confirmed cases.

In the absence of saliva, serum may be used for the purpose. Rubella and parvovirus B19 infection may cause false-positive IgM ELISAs in serum samples though paired sera (acute and convalescent) can be used to detect a fourfold rise in IgG antibody by complement, and serum is the sample of choice to assess immune status of contacts through enzyme immunoassays with detection of IgM and IgG.

Mouth swabs can be used for PCR if collected within 6 days of the onset of rash, but a negative PCR result does not exclude a diagnosis of measles. Throat swabs, nasopharyngeal aspirate, urine and a blood sample in EDTA can be used for PCR if collected within 6 days of the onset of rash. The best yield is

obtained when samples are collected within the first 3 days of the rash and become unreliable later.^{11–13}

How should a case of suspected measles be managed?

Patients suffering from measles are likely to find their way unannounced into the ED, children's ED or outpatient practice setting. Detering attendance based on reported symptoms may be possible but is fraught with risk because of the wide-ranging differential diagnoses, which include some serious and time-sensitive conditions. If measles is suspected at initial assessment, the patient should be transferred to an isolation area for further management. Treatment is targeted at symptom control, with oral fluids and antipyretics. A comprehensive clinical assessment, including otoscopy and chest examination, will identify complications and the need for antibiotics for superadded bacterial infections. Antiviral agents and prophylactic antibiotics are of no value. Given that vitamin A deficiency predisposes to severe and complicated measles, two oral doses of vitamin A 200 000 IU (100 000 IU if age 6–11 months, 50 000 IU if under 6 months) is recommended for all children with acute measles and to all cases of severe infection with measles. A third dose is given 2–4 weeks later.¹⁴

Disposition is usually to home in the absence of complications. Prevention of spread of infection to vulnerable household contacts is an important consideration and must be discussed with parents or care givers. Immunisation with MMR should be offered as soon as practicable, since vaccination induces antibody response more rapidly than infection and to cover mumps and rubella. Two doses separated by at least a month ensures maximal antibody levels.

The disease is notifiable and local health protection teams must be informed.

How contagious is measles?

Measles is highly contagious, and infection is almost inevitable in unimmunised individuals exposed to a case unless stringent precautions are taken. Cross-infection is by airborne spread, and the period of infectivity is from the last 2 days of incubation until 4 days after the rash appears. Patients with suspected measles should be nursed in an isolation area with good ventilation, and staff and visitors, including those with a reliable history of vaccination, should wear disposable aprons and gloves and use a well-fitting N95 respirator mask. Members of staff who are known to have no measles immunity should not have any contact with cases. Postexposure prophylaxis with intravenous immunoglobulin should be considered for selected contacts (infants, immunocompromised patients and pregnant women) known or thought likely to be measles antibody negative.¹⁵

After discharge from the ED, the isolation cubicle 'terminal cleaning' must be undertaken before receiving another patient into the room. The procedure is undertaken by nursing and cleaning staff, properly attired in personal protective equipment, under the guidance of the Infection Prevention and Control team. Standard operational procedures govern the use of materials and the techniques for ensuring proper decontamination of equipment and the patient environment.

QUESTIONS (3)

- i. Is the vaccine effective? When is it given?
- ii. How should measles exposure be managed where the immunisation history is uncertain?
- iii. What precautions should be taken when travelling to an area of relatively high incidence?

ANSWERS (3)**Is the vaccine effective? When is it given?**

The most common MCV is available as part of the combined MMR product, containing freeze-dried live, attenuated strains of measles, mumps and rubella viruses. The WHO recommends two doses of a MCV by 2 years of age, and the target for uptake is 95%. A single dose provides 90% protection to the individual, while the second dose prevents onward measles transmission. A killed measles virus vaccine became available in 1963, and an improved product emerged in 1969. People born before 1970 are likely to be immune by exposure to measles. The MMR vaccine was introduced in 1989, and therefore those born before 1990 may not have been fully immunised.

In 2018, around 85% of children worldwide had received one dose, and in countries where routine immunisation includes a second dose, 67% had received two doses of MCV by their second birthday. Rates of uptake in the UK are falling and remain slightly below target at just over 91%.¹⁶ The immunisation schedule for MMR is a first dose shortly after the first birthday and a second dose prior to starting primary school: at 40 months in the UK, 4 years in Australasia and 4–6 years of age in North America. Infants may be vaccinated at 6 months of age if exposed to a case, or in the context of an outbreak locally. MMR is not given to younger infants because transplacentally acquired antibodies will render the vaccine ineffective.

How should measles exposure be managed where the immunisation history is uncertain?

There is the opportunity to 'catch up' where an individual has not completed the recommended immunisation schedule. The two doses are given at least a month apart. MMR vaccine can be given irrespective of a history of measles, mumps or rubella infection, or vaccination. There are no ill effects from immunising such individuals because they have pre-existing immunity that inhibits replication of the vaccine viruses. In an outbreak where there is doubt about an individual's immunisation status, and the where the patient's family doctor is uncertain, it is safe to offer MMR. The vaccine is well tolerated, sometimes causing a mild and short-lived form of measles (or rubella) at 2 or 3 days. MMR does not cause autism.

Women who are unimmunised and planning pregnancy should receive MMR vaccine and should guard against pregnancy for at least 28 days after the immunisation.¹⁷ Measles in pregnancy carries a high risk of complications in mother and baby, and the vaccine will also protect against the congenital rubella syndrome. The vaccine is not known to present any risk in pregnancy, but data are lacking and at present it is not recommended. Breast feeding is not a contraindication to vaccination.

What precautions should be taken when travelling to an area of relatively high incidence?

Measles is common in Africa, especially in Nigeria, in China, the Philippines and the Middle East, including Yemen. The highest rates in Europe are seen in Serbia, Romania and Ukraine, with intermediate rates in UK, Germany and Italy. Reported cases are relatively few in North America, Australia and New Zealand, but the incidence is rising in recent years.^{5 6}

Individuals of all ages who are not immunised who are travelling to endemic areas should be fully immunised, including babies from 6 months of age who should receive a dose of MMR prior to departure. As a follow-up, these infants should be immunised at the recommended ages again with two doses according to the schedule. Children who are travelling and have

already received one dose of MMR at the routine age should have the second dose brought forward to at least 1 month after the first. If the child is under 18 months of age and the second dose is given within 3 months of the first dose, then the routine preschool dose (a third dose) should be given in order to ensure full protection.¹⁷

CASE CONCLUSION

Blood results were received 3 days after initial presentation. The serum was positive for measles IgM, indicating recent infection, and measles RNA. IgG was negative. Measles PCR detected measles genome and sequencing confirmed genotype D8. The child was improving on his mother's account at that time and was quite well on enquiry at 3 weeks after presentation.

DISCUSSION

The recent case presented here demonstrates that measles remains an important disease even in those countries with good uptake of vaccination. The disease is encountered most often in young children but can affect any age. It is seasonal but can occur at any time. It presents most often in travellers visiting or returning from endemic regions but is also seen in locally based individuals. Immunisation provides very effective protection against measles, but the vaccination history may be unreliable. The diagnosis is clinical, and treatment is symptomatic. Investigations are confirmatory, and serotyping is important for surveillance and control of outbreaks. Disposition is determined by illness severity but in any event must ensure isolation of cases from contacts susceptible to infection and protection of health-care professionals. Measles is a notifiable disease.

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