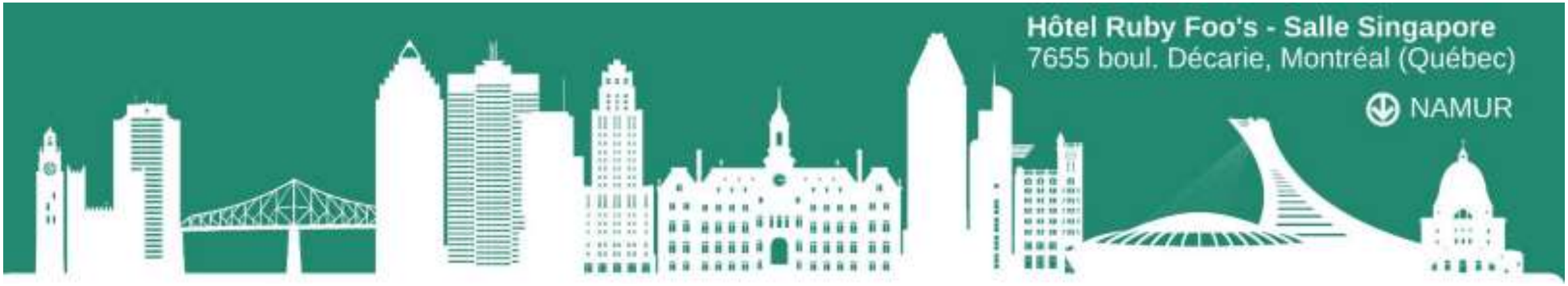


When even “measles” is not…measles

Lessons learned during an outbreak

Christos Karatzios MD

Assistant Professor of Pediatrics/Division of Infectious Diseases/Montreal Children’s Hospital

Membre Associé/Département de Pédiatrie/Université de Montréal/Immunologie spéciale/CHU-Ste Justine

Centre universitaire de santé McGill
McGill University Health Centre

JOURNÉE D’ÉDUCATION 2024
PROGRESSER PAR L’ENGAGEMENT ET L’INNOVATION
pci Qc
19 VENDREDI avril

EDUCATION DAY 2024
PROGRESS THROUGH ENGAGEMENT & INNOVATION
pci Qc
FRIDAY April 19

Disclosures

- I do not have any conflicts of interest.
- All pictures in this presentation were taken and are being used with the consent of the patient’s mother.

The root of the word comes from…

- Greek
  - Etymology
  - From Byzantine Greek ἱλαρά (*hilará*), feminine form of Ancient Greek ἱλᾰρός (*hilarós*, “happy, cheerful”), a euphemistic name for the disease. The root of the word/name hilarious/Hillary is from this.
    - https://en.wiktionary.org/wiki/%CE%B9%CE%BB%CE%B1%CF%81%CE%AC

- The modern name Measles comes from an ancient Arabic word, “miser”, which means the "unhappiness of lepers." Measles was also historically sometimes known as "little leprosy”.
  - https://cepi.net/paramyxoviruses#:~:text=The%20modern%20name%20Measles%20comes,known%20as%20%22little%20leprosy%E2%80%9D.

Fever and rash in a toddler…

- 15 month old boy, previously well (March 2024)
  - MMR-V not given yet.
  - Mother is a health care worker at a Family Medicine clinic in Montreal
  - Montreal is the epicenter of a Quebec-wide measles outbreak in early 2024
    - active cases being reported in the city in March 2024
- First dose MMR: March 5, 2024
- Fever and increased rhinorrhea starting March 21-22, 2024
  - Saw a doctor (not the primary MD) at the clinic on March 22, 2024
  - Diagnosis: non-specific viral illness.
  - Sister had diarrhea the week before.
- Rash started March 22, 2024 but was not-specific
  - Started upper body; mom not sure if face first
  - On March 24, 2024 the primary MD saw the pictures via text but didn't think anything of it.
- The mother brought the infant in on March 25, 2024 suspecting measles
  - Seen by primary MD
  - The rash looked more suspicious for measles.
  - Primary MD called me for advice for disposition and testing.

March 22, 2024

Fever X 1 day

New rash:

- Started on upper body
- Non-specific

Diagnosis:

- “viral”.

March 25, 2024

Fever X 4 days

Rash:

- More intense now
- Palmar

No conjunctivitis

No coryza

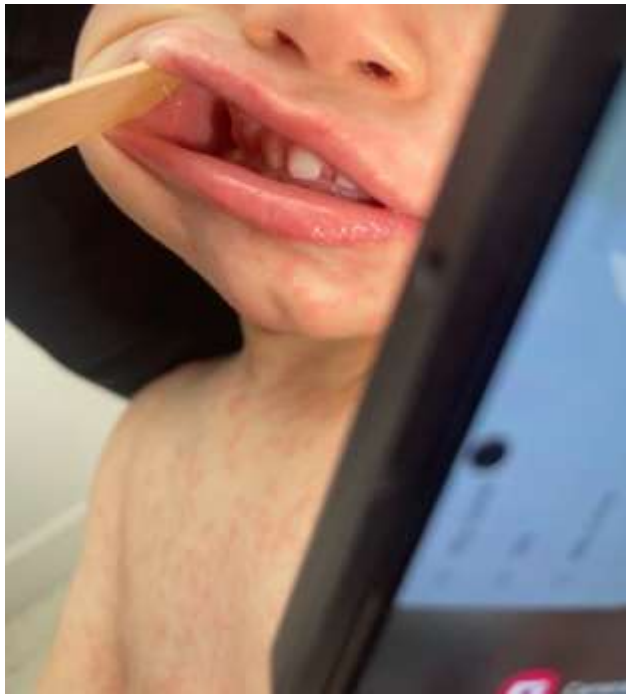
- Mild congestion

Diagnosis:

- “viral” but...looks like it could be measles!

March 25, 2024

Koplik spots!



Questions asked and advice given…

- No known measles contact
- Does not go to daycare
- Siblings are vaccinated against measles X 2
- My diagnosis:
  - Attenuated form of measles? Bizarre story but hear me out:
    - Was incubating measles when he was vaccinated (became ill 16 days later)
    - Got infected with measles while he was forming immunity from the vaccine
    - Another virus? Enterovirus vs adenovirus (sister had diarrhea the week before)
- Advice:
  - Better safe than sorry.
  - Put surgical mask on child and…
  - Come to MCH ER for:
    - Measles testing (Nasopharyngeal (NP) swab for measles PCR, measles IgG/IgM, urine measles PCR(?))
      - Would not rely on measles IgM though.
    - NP swab for other respiratory viruses
    - Call the ER ahead to prepare negative pressure room

More questions asked and more advice given…

- The patient and his mom were in the general waiting room of the clinic on March 21, 2024.
  - The whole visit from arrival to departure: about an hour.
- The patient and his mom entered through the back door of the clinic on March 25, 2024 and were placed in a neutral pressure room with the door closed about 30 min before I was called.
  - They may have stopped in mom's office for a few minutes before.
  - The whole visit from arrival to departure: about an hour.
- Start taking down the names and contact information of all vulnerable patients/staff in the clinic areas for March 21 and 25, 2024
  - From time of arrival to 2 hours after departure of the patient
- Call Montreal Public Health

In MCH ER…

- Placed in isolation (negative pressure room) upon arrival
- Afebrile and well-looking
- Story and exam corroborated as before
- Tested for measles and sent home to remain at home until results in (despite it being 4 days after onset of rash).

- Testing done:
  - Measles IgM: 3.8
    - **POSITIVE (>1.10)**
  - NP swab for measles PCR
    - **POSITIVE**
    - **PCR for genotype A (measles vaccine virus): MMR vaccine strain!**

Ultimate diagnosis…

- Post MMR vaccine “measles”
  - Not infectious to others. Kids usually do very well if not SEVERELY immune compromised.
  - Fever and a rash can be seen in up to 5% of MMR vaccine recipients usually 7-10 days up to 1 month after vaccination.
    - Usually though it is not as extensive as in our patient
  - Koplik spots are rarely seen (only 1 reported in the literature – more on this soon).

- Referring physician and Montreal Public Health were contacted and investigations into other contacts stopped.
- Patient now out of quarantine.
- Can receive second dose of MMR-V vaccine at the appropriate time after the first (likely won’t have another reaction like this because is now immune to measles).

What happens when we look for measles during an outbreak?

- We will find not only measles but also “measles” (i.e. vaccine-related)
- In a recent surveillance study out of the US:

Morbidity and Mortality Weekly Report

Implications of Measles Inclusion by Commercial Syndromic Polymerase Chain Reaction Panels — United States, May 2022–April 2023

Christine M. Thomas, DO[1,2,*]; Amanda Hartley[1,*]; Ann Schmitz, DVM[3,4]; Heather D. Reid[5]; Susan Sullivan, MS[6]; Elise Huebner, MS[7]; Meredith Robinson, MS[8]; Adria Mathis, MSPH[9]; Mary-Margaret A. Fill, MD[1]; Kara J. Levinson, PhD[10]; Tim F. Jones, MD[1]; William Schaffner, MD[11]; Caitlin N. Newhouse, MD[1]; John R. Dunn, DVM, PhD[1]

- May 2022 – April 2023
- When measles PCR is included in syndromic nasopharyngeal PCR tests for “rash infectious diseases” NOT during a measles outbreak:
  - 1,548 tests done
    - 1.1% (n=17 children; range: 1-6 yrs old; median: 1 yr old) were positive for measles PCR
    - Out of these 17 positives, 14 had measles vaccination/case history available
      - 13 were vaccinated within 21 days (range: 8-115 days ago; median: 12 days ago)
      - 8 had fever and/or 4 had cough and coryza
      - No epidemiological risk for measles exposure for any child

Thomas CM, Hartley A, Schmitz A, et al. Implications of Measles Inclusion by Commercial Syndromic Polymerase Chain Reaction Panels — United States, May 2022–April 2023. MMWR Morb Mortal Wkly Rep 2024;73:260–264. DOI: http://dx.doi.org/10.15585/mmwr.mm7312a3.

But…
(aka “Limitations”)

Don’t stress me.

- What if it is a mixed infection? Theoretically possible.

- Any other conditions/viral illnesses causing Koplik-like spots?
  - Fordyce spots/aphthae
  - Aphthous ulcers
  - Parvovirus B19 disease

} Unlikely

What about Koplik spots?

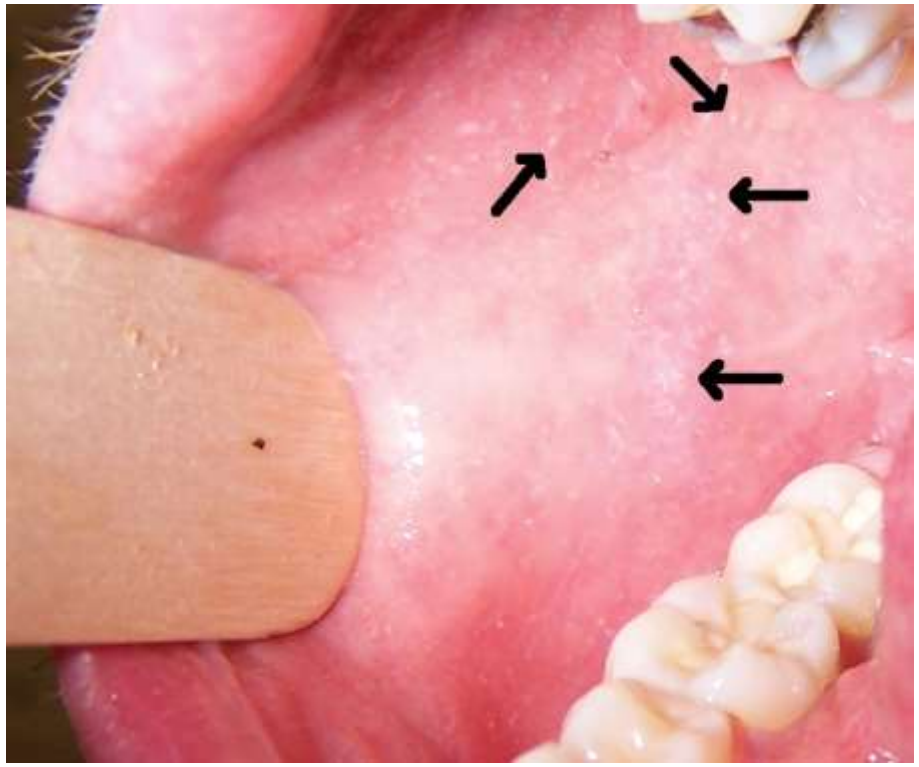


Figure 1: Koplik spots (arrows) in a 30-year-old man with measles, observed on the second day of the rash.

Koplik spots are highly characteristic of the prodromal phase of measles and can often be identified before the onset of the rash. Since they were originally described in 1896,[2] these millimetric, erythematous, white or grey specks on the buccal mucosa have been regarded as a pathognomonic feature of measles.[3] **They typically appear opposite to the upper molars a couple of days before the rash, occasionally extend to the whole buccal mucosa, then disappear as the rash develops. Koplik spots can be noted in at least 50%–70% of patients with measles if examination is timely.[3] Occasionally, they also occur on the conjunctiva, the vaginal mucosa or the gastrointestinal mucosa.**

Steichen O, Dautheville S. Koplik spots in early measles. CMAJ. 2009 Mar 3;180(5):583. doi: 10.1503/cmaj.080724. PMID: 19255085; PMCID: PMC2645467.

What about Koplik spots?

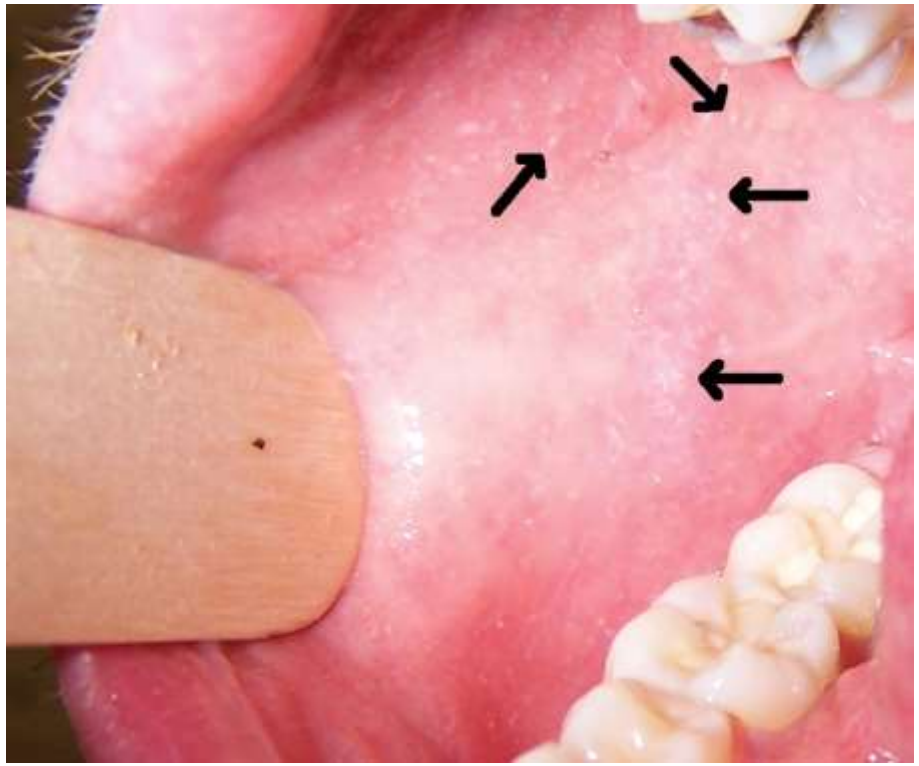


Figure 1: Koplik spots (arrows) in a 30-year-old man with measles, observed on the second day of the rash.

The onset of measles as described by Koplik in 1896

The first twenty-four to forty-eight hours of the invasion of measles is marked by a suffusion, slight or marked, of the eyes, and the conjunctiva at the nasal canthus is not only reddened but also slightly redundant. There is, at this stage, a slight febrile movement; there may be a cough or some little sneezing; the mother has noticed nothing except that the infant or child has a slight fever. **At this period the eruption on the skin has not made its appearance.** In the majority of cases there is no suspicion of any exanthema. In a few cases there is an indistinct spotting around the lips and alae nasi, but no eruption.

The mouth — If we look in the mouth at this period we see a redness of the fauces; perhaps, not in all cases, a few spots on the soft palate. On the buccal mucous membrane and the inside of the lips, we invariably see a distinct eruption. It consists of small, irregular spots, of a bright red colour. In the centre of each spot, there is noted, in strong daylight, a minute bluish white speck. **These red spots, with accompanying specks of a bluish colour, are absolutely pathognomonic of beginning measles, and when seen can be relied upon as the forerunner of the skin eruption.**[2]

Steichen O, Dautheville S. Koplik spots in early measles. CMAJ. 2009 Mar 3;180(5):583. doi: 10.1503/cmaj.080724. PMID: 19255085; PMCID: PMC2645467.

Koplik H. The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal mucous membrane. *Arch Pediatr* 1896;13:918-22.

Variations in Vitamin D Production Could Possibly Explain the Seasonality of Childhood Respiratory Infections in Hawaii

To The Editors:

The report on the rates of hospitalization of children younger than 5 years of age for bronchiolitis, respiratory syncytial virus (RSV), and pneumonia[1] is interesting. These 3 respiratory infections have peak rates in winter and lower rates in summer. In addition, the rates have considerable variation by ethnic background. While some discussion was devoted to explaining the findings, no firm conclusions were reached. In this letter, we suggest that variations in vitamin D3 production with respect to season and skin pigmentation could explain the general features of the data.

There are 3 p
respiratory viral infe
mon in winter than
perature, low relati
solar ultraviolet-B
temperature constr
capillaries so that fe
are near the surface
isms. Low relative
easier for exhaled v
UVB reduces vitam
Vitamin D3 induces
cathelicidin, LL-37
antimicrobial prope
hoc analysis of a r
trial of vitamin D
postmenopausal bl
New York State fou
tion against the co
enza.[4] A manuscrip
fits between monthl
rus and norovirus in
monthly variations
min D3 (calcidiol)
submitted].

Because Hav
solar UVB doses a
clouds than by sola
fall peaks in Decer
is at a minimum in
cloud cover corres
lar UVB doses wo

and reach a nadir at the end of the year. There is a strong inverse correlation between hospitalizations for bronchiolitis and RSF and rainfall.[1] Tourists from colder climates are probably an important source of infection as well.

The variations of the 3 respiratory infection rates versus ethnic background provide further support for a role of vitamin D. The skin pigmentation for the races are likely ordered in ascending fashion as follows: white, Japanese, Chinese, Other Asian, Filipino, Hawaiian, other Pacific Islander, and black.[5] Other than for black children, for whom the number of cases is low, the relative hospitalization rates are, in general, directly correlated with skin pigmentation.

The hypothesis that vitamin D3 production rates are related to childhood respiratory viral infections in Hawaii would be easy to test by measurements of serum 25-hydroxyvitamin D at the time of hospitalization and to correct with vitamin D3 supplementation, not only for young children, but for people of all ages, and espe-

discharge for 24 hours. Ten days before he had received the trivalent measles-mumps-rubella (MMR) vaccine. Fever was absent. The mother noted the presence of a suspected stomatitis associated with poor appetite for 24 hours. The thoracic and abdominal examination was normal and no lymphadenopathy was detected. The buccal and inner labial mucosa appeared normal and the lip was slightly reddened. Around the second molars bilaterally we noted the presence of small irregular bluish-white spots. These resembled Koplik spots of measles. We decided on observation awaiting the appearance of rash. We prescribed only an antihistamine. After 24 hours, the child developed a nonspecific exanthem over the entire body that persisted for 2 days. The Koplik spots disappeared concomitant with the onset of rash.

Fever is the commonest side effect of measles vaccination, and approximately 5% of vaccinees develop

The Pediatric Infecti

Koplik Spots in a Measles-Vaccinated Child

To the Editor:

Recently, a 15-month-old boy came
our observation, with an illness characterized by malaise, irritability, and nasal

persisted for 2 days. The Koplik spots disappeared concomitant with the onset of rash.

Fever is the commonest side effect of measles vaccination, and approximately 5% of vaccinees develop a mild rash. Normally fever and exanthem occur 7–10 days after the vaccination. We have not found a previous report of Koplik spots in vaccinated children.[1–3]

Ilaria P. Porta, MD
Azienda Sanitaria Locale della Valle d'Aosta
Aosta/Aoste, Italy

Porta IP, Bertone C, Baldassare E. *The Pediatric Infectious Disease Journal* • Volume 27, Number 9, September 2008

Take home points

- **Measles**: bad
- **Vaccine measles**: not bad but it's a nuisance
- **Vaccine measles**: usually no Koplik spots BUT who really knows because these kids will not present to medical care! So perhaps it is more common than we think.
- In any context (measles outbreak or not): **when you look for measles you will find it**.
  - Many (if not most) will be vaccine-related.
    - Especially if the child is vaccinated recently
    - No epidemiological risk factors for measles exposure
  - Therefore, a careful **history** is <u>just as important</u> as the **test result**.
    - Increases your index of suspicion for vaccine-related measles
    - Decreases stress on Public Health and everyone involved.
    - Theoretical risk of a mixed infection (vaccine plus wild-type strains).

Measles is Hilarious!

Thank you!

Questions?