Emerging and re-emerging threats in a post pandemic world

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No conflicts of interests to disclose

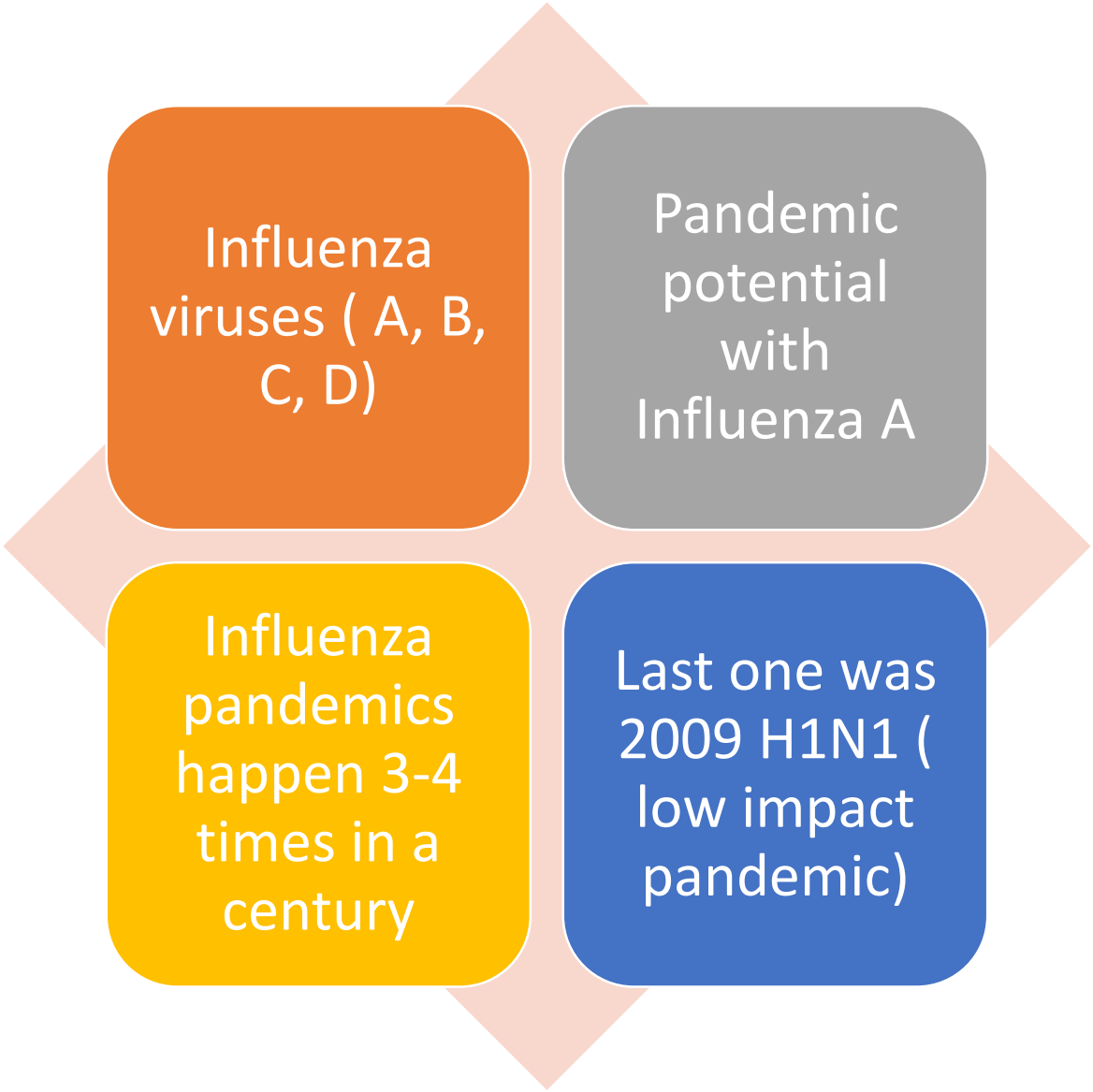
Agenda

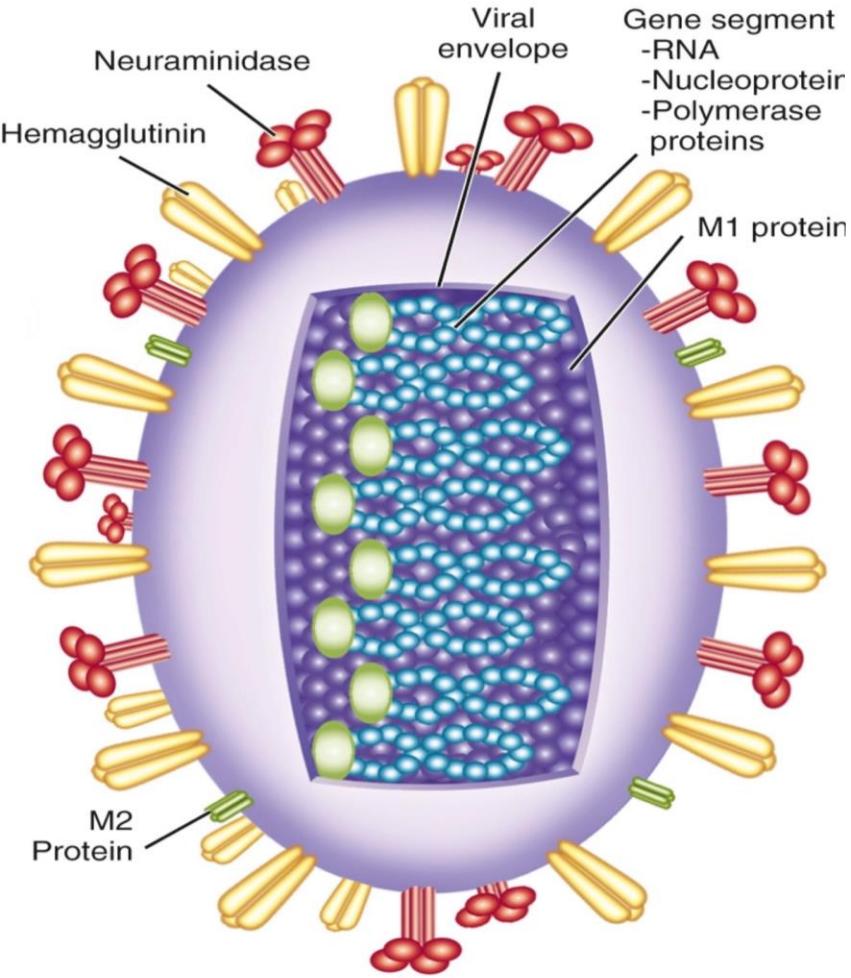
- H5N1 HPAI -> current state and future risk
- Measles update

Influenza History

- “ Influence”
- *Hemophilus influenzae* (thought to be etiology for a long time)
- Reports of pandemics in the past (15^{th} , 16^{th} cenutries, 1918, 1957, 1977, 2009 etc)
- Isolated finally in 1933 (A) → ferrets
- Flu B in 1939 and Flu C in 1950

Influenza Viruses



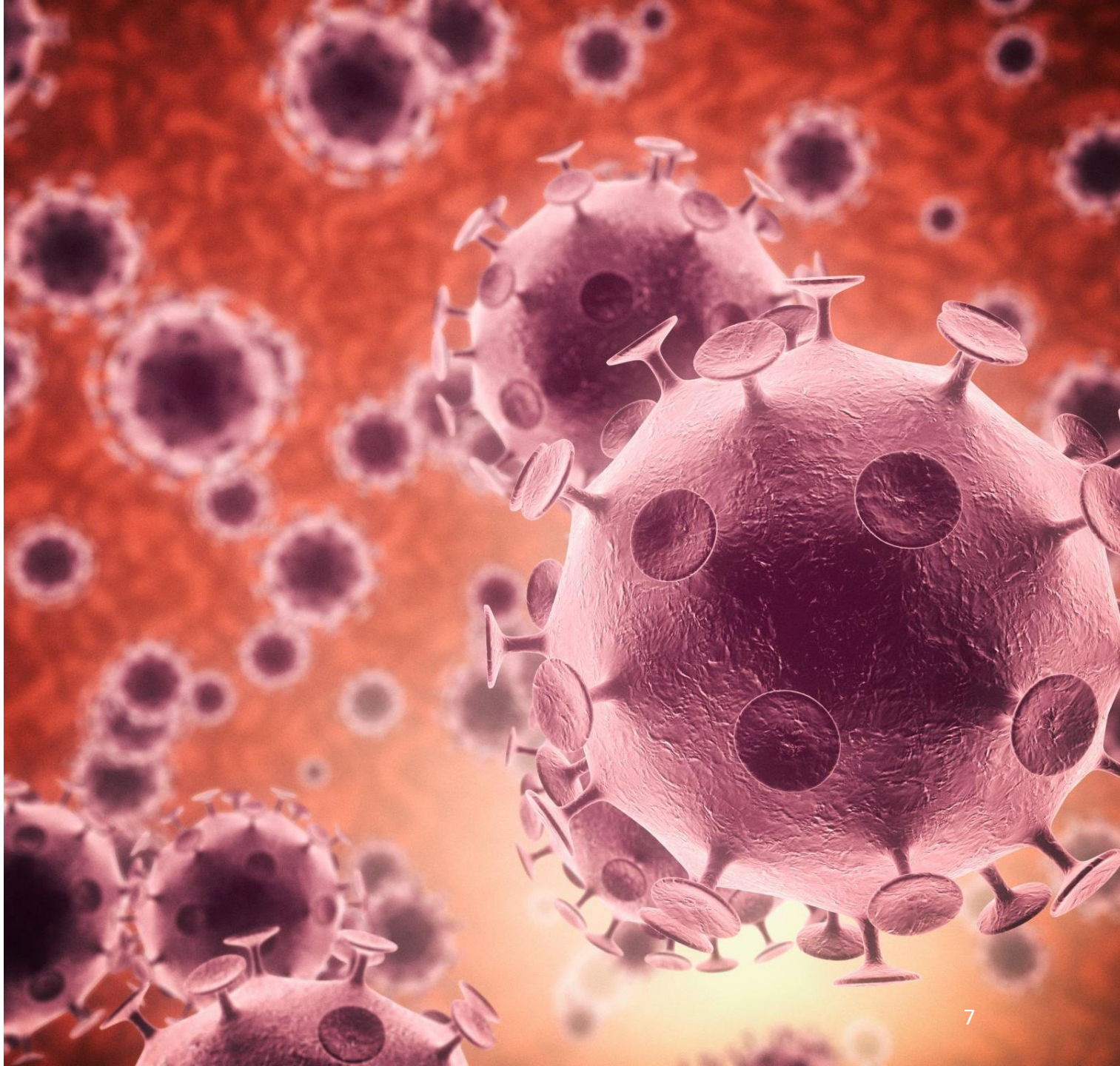


The Virus (Influenza A)

- RNA viruses, belong to birds (waterfowl)
- Plastic genome, easily adaptable
- Gene reassortment (mixing of gene segments between different subtypes of influenza viruses)
- Antigenic drift (small changes, reason for yearly flu shots)
- Antigenic shift (major change, only happens in type A, causes pandemics)

Influenza A Viruses

- Further classified by H and N antigen types
- There are 16 H types and 9 N types known
- Further clades and subclades



Pathogenesis

- Hemagglutinin for entry
- Neuraminidase for exit and destruction
- Avian and human influenza viruses tend to have different receptor localization

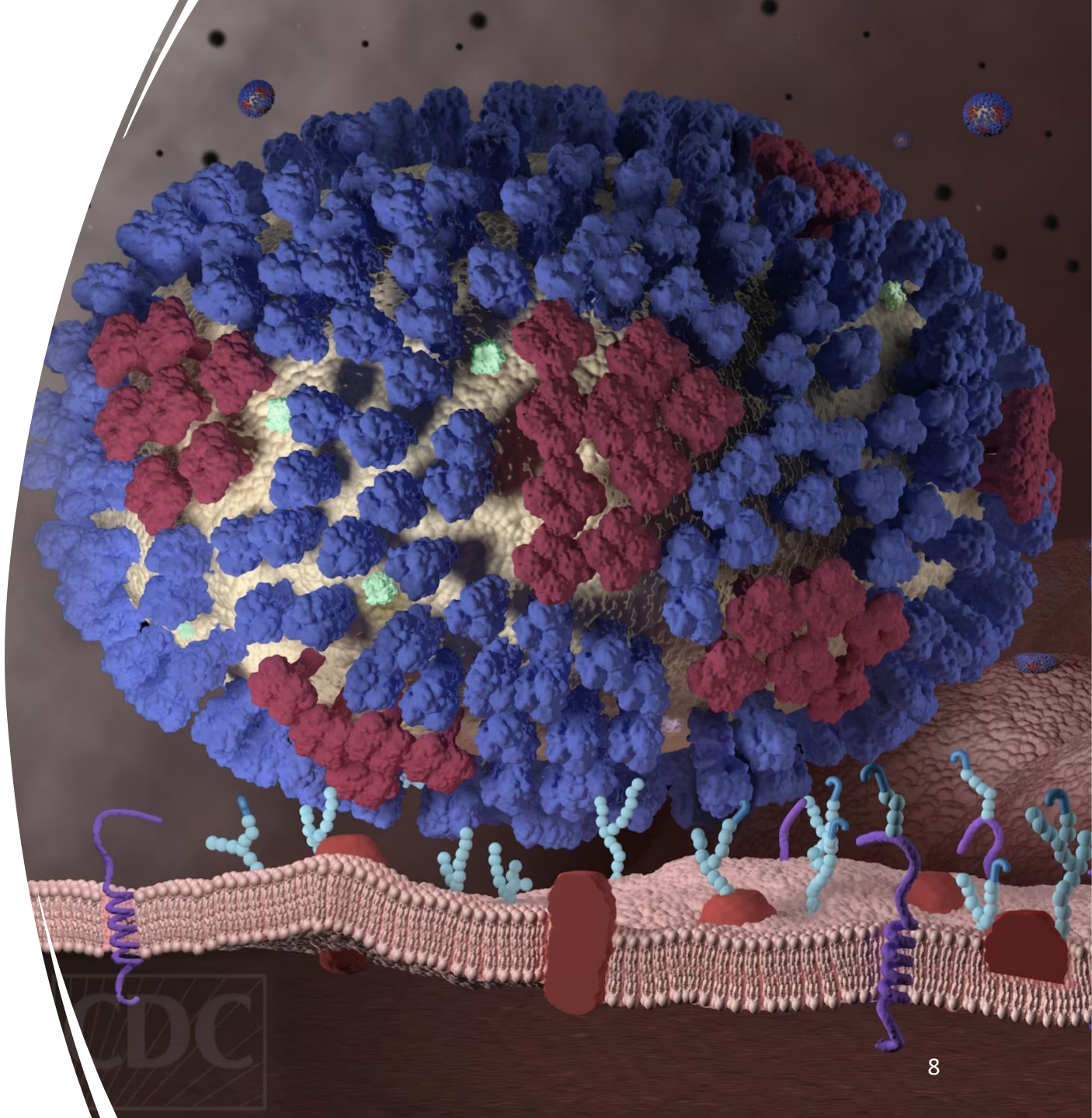
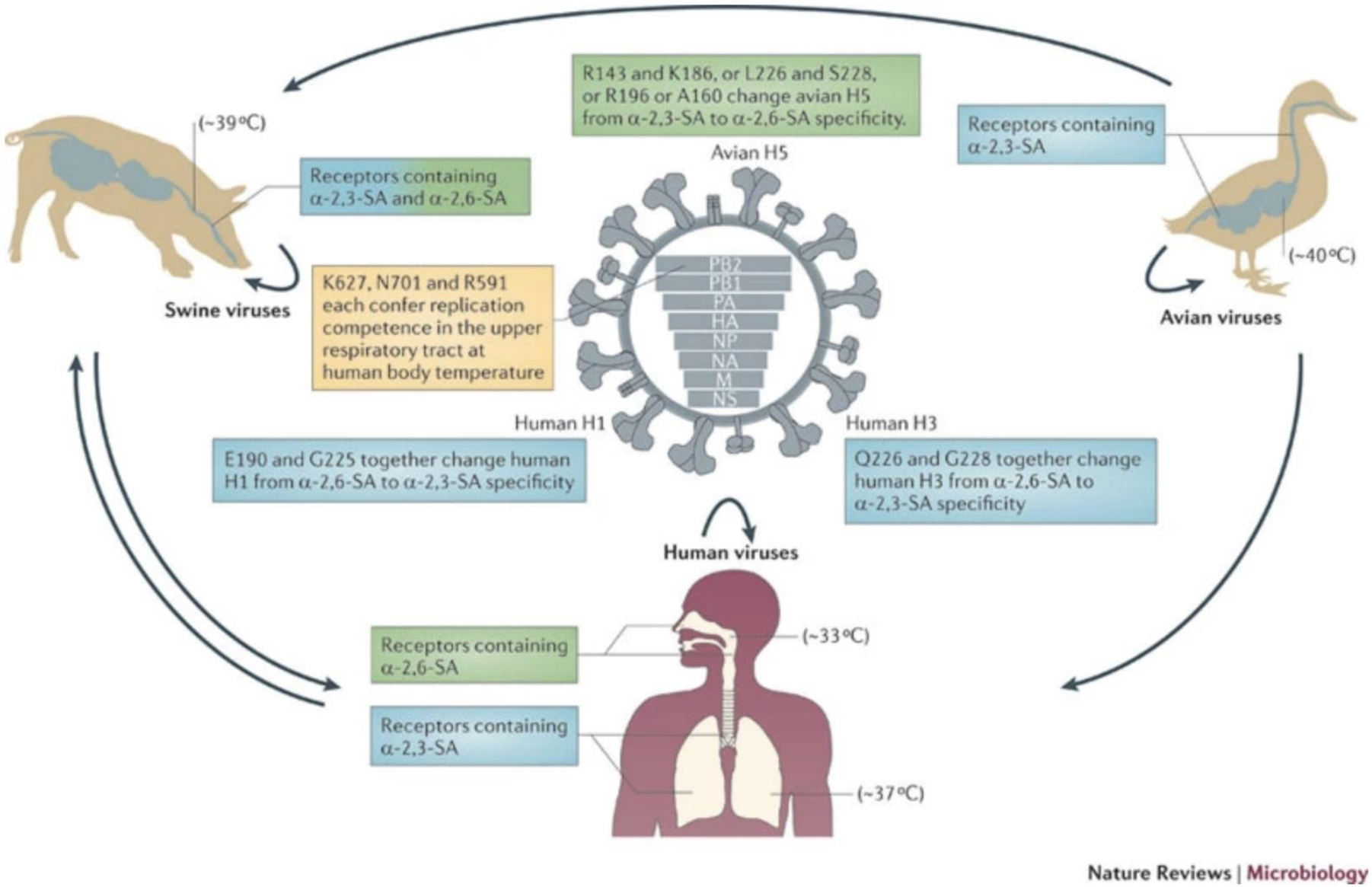


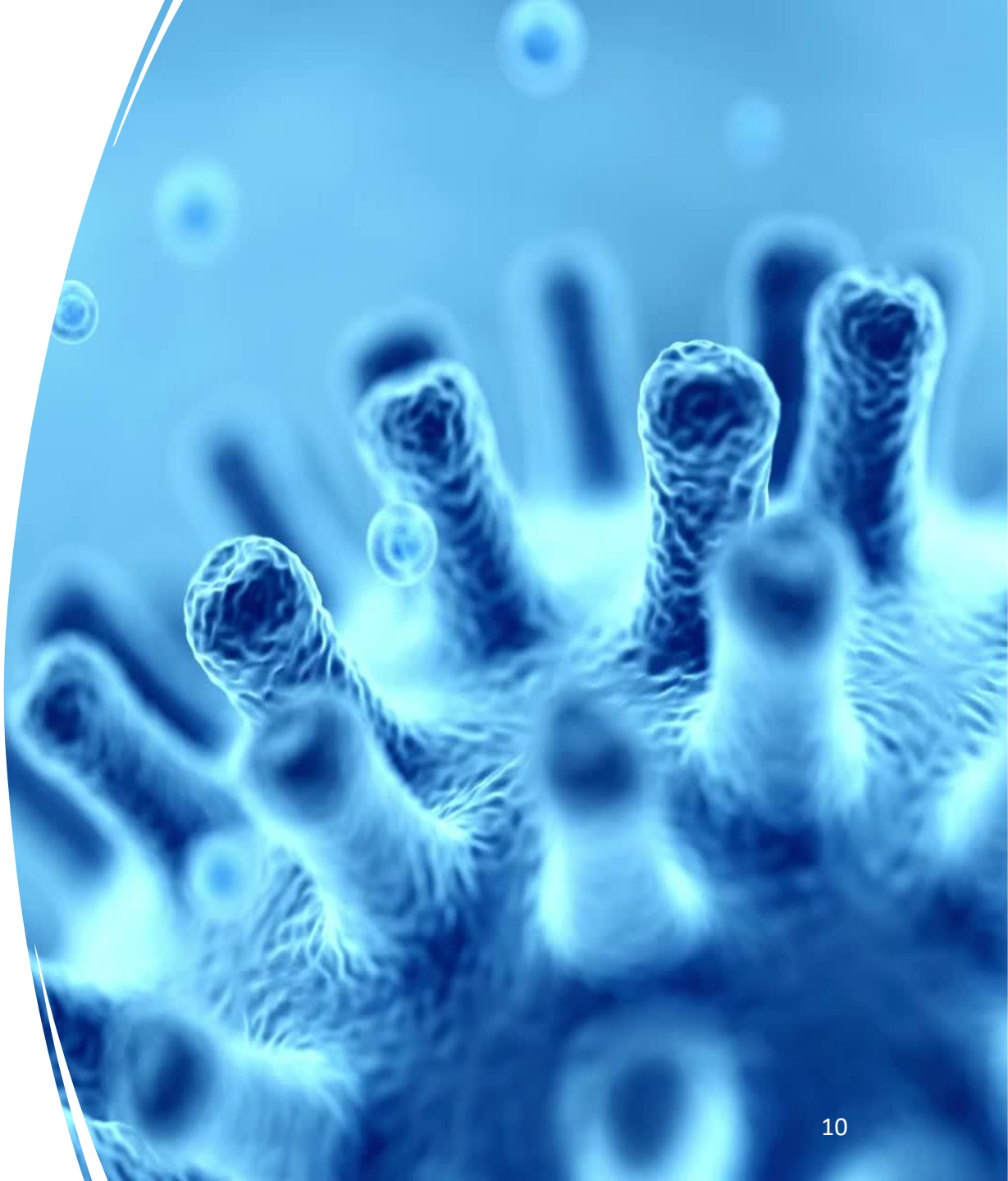
Figure 3: Influenza A virus tropism.

From: [Influenza A viruses: new research developments]



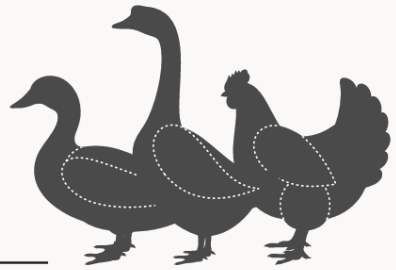
Evolution

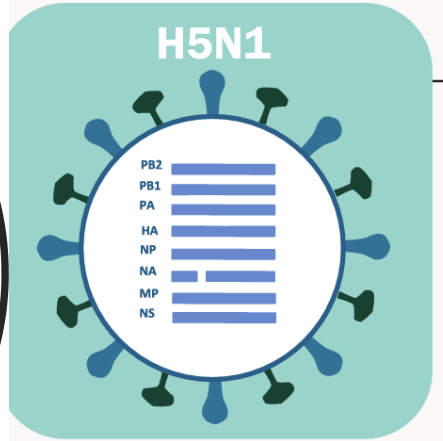
- Mixing in different animals (Swine, Cattle) infection with both human and avian viruses
- In 2009 mixing happened within certain swine species → Novel H1N1
- One subtype then gains survival advantage



A novel virus emerges

Emergence and Evolution of H5N1 BIRD FLU



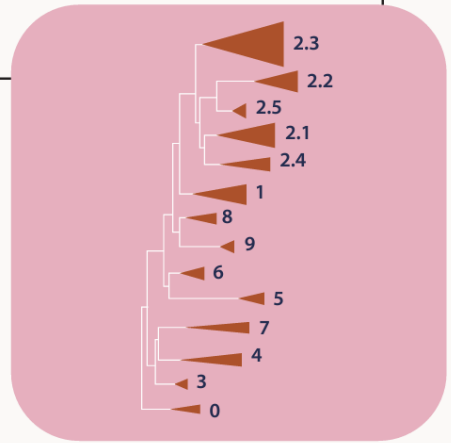


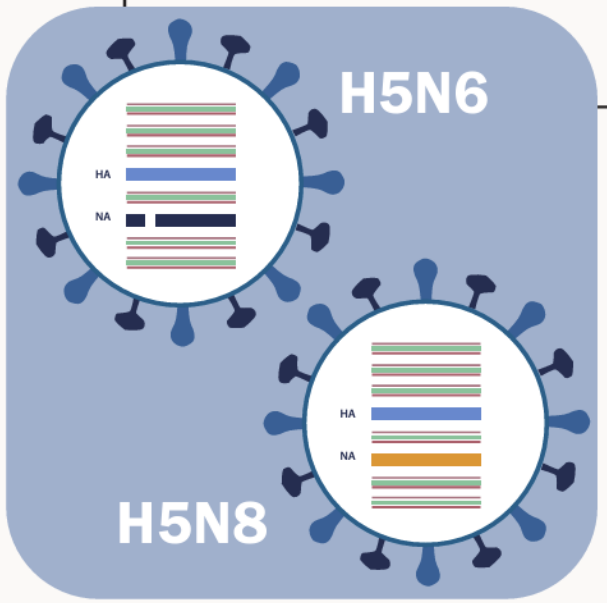
1996-1997 H5N1 bird flu virus first detected

In 1996, highly pathogenic avian influenza H5N1 virus is first identified in domestic waterfowl in Southern China. The virus is named A/goose/Guangdong/1/1996. In 1997, H5N1 poultry outbreaks happen in China and Hong Kong with 18 associated human cases (6 deaths) in Hong Kong. This virus would go on to cause more than 860 human infections with a greater than 50% death rate.

H5N1 spreads *2003-2005*

For several years, H5N1 viruses were not widely detected; however, in 2003, H5N1 re-emerges in China and several other countries to cause widespread poultry outbreaks across Asia. In 2005, wild birds spread H5N1 to poultry in Africa, the Middle East and Europe. The hemagglutinin (HA) gene of the virus diversifies into many genetic groups (clades). Multiple genetic lineages (genotypes) are detected.



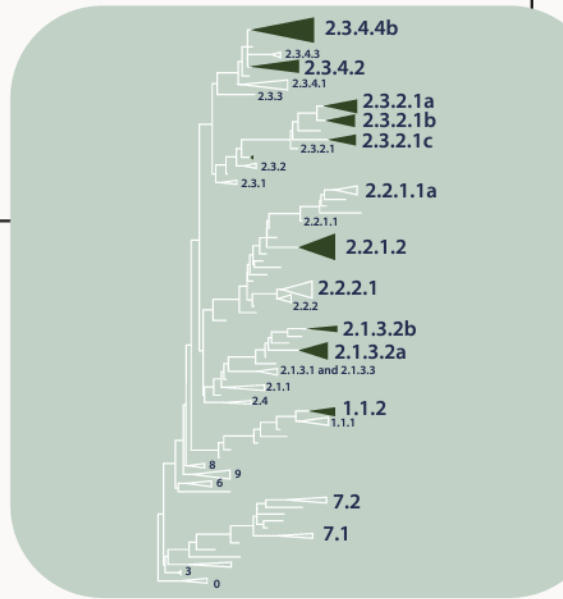


2014-2016 H5N6 and H5N8 viruses emerge

Gene-swapping of H5 viruses from poultry and wild birds leads to emergence/detection of H5N6 and H5N8 virus subtypes. HA diversifies further into clade 2.3.4.4 in Asia, Africa, Europe, the Middle East and North America. H5 viruses with various neuraminidase (NA) genes continue to be detected, including in U.S. wild birds and poultry.

2.3.4.4b viruses spread widely 2018-2020

H5N6 and H5N8 viruses become predominant globally, replacing the original H5N1 viruses. As of 2022, there have been more than 70 H5N6 human infections and 7 H5N8 human infections reported. The H5 HA diversifies further into clade 2.3.4.4b which becomes predominant in Asia, Africa, Europe, and the Middle East.



H5N1 clade 2.3.4.4b

2021-2023 H5N1 found in Canada, US

A new H5N1 virus belonging to clade 2.3.4.4b with a wild bird adapted N1 NA gene emerges. Clade 2.3.4.4b H5N1 viruses become predominant in Asia, Africa, Europe, and the Middle East by the end of 2021. The virus is detected in wild birds in Canada and the United States in late 2021. In February 2022, the virus begins causing outbreaks in U.S. commercial and backyard poultry. Rare, sporadic human infections with this H5N1 virus are detected, as well as sporadic infections in mammals. More information is available: https://www.cdc.gov/flu/avianflu/inhumans.htm.

30646-B

Transmission of H5N1

Bird to bird (wild birds to domestic poultry)

Bird to mammal

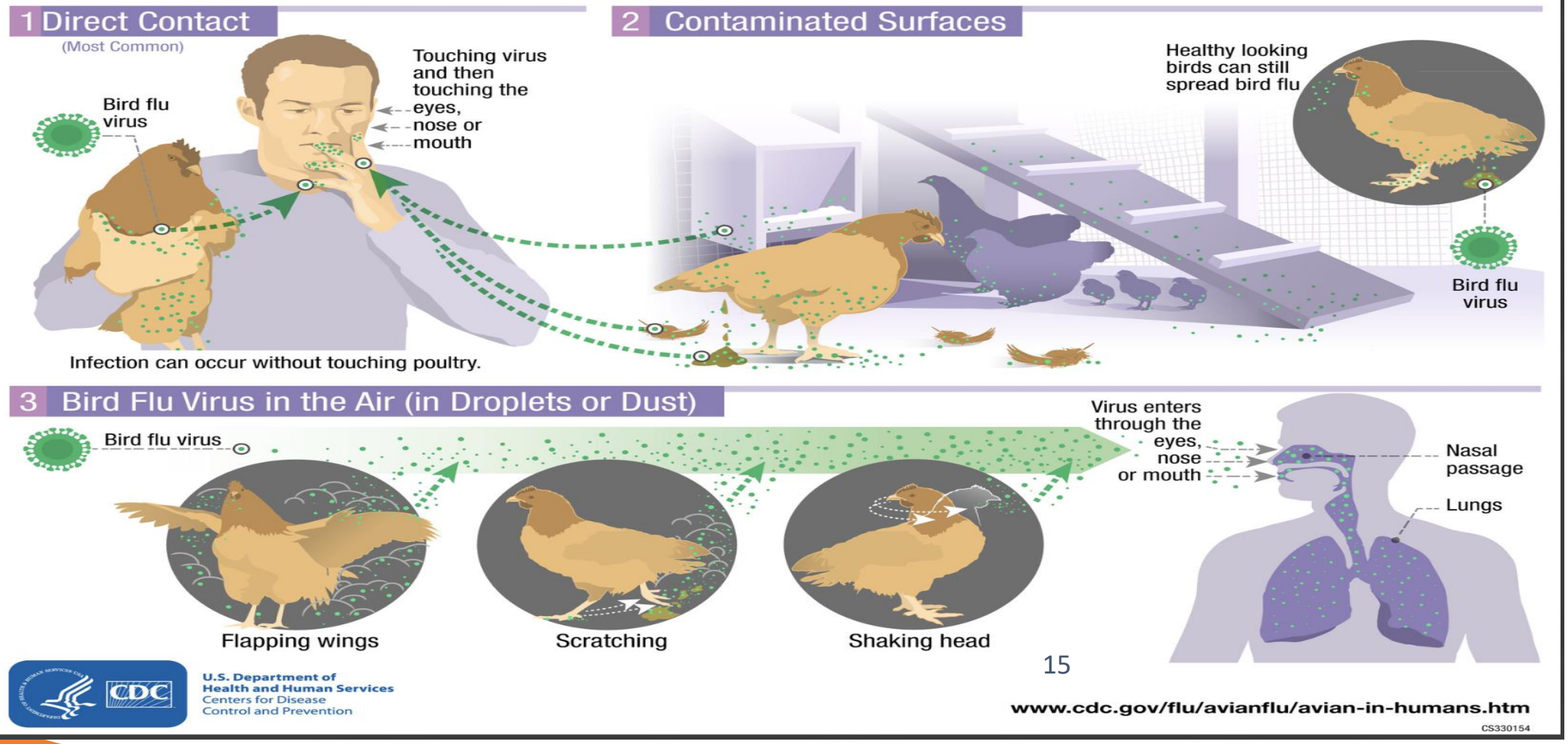
(identification amongst pets, decimation of seal populations)

Human to human (rare, mostly common exposures and clusters)

Mammal to mammal (domestic cattle)

How Infected Backyard Poultry Could Spread Bird Flu to People

Human Infections with Bird Flu Viruses Rare But Possible



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

www.cdc.gov/flu/avianflu/avian-in-humans.htm

CS330154

Highly Pathogenic Avian Influenza A (H5N1) Virus Infection Reported in a Person in the U.S.

CDC's Risk Assessment for the General Public Remains Low

Print

Press Release

For Immediate Release: Monday, April 1, 2024
Contact: Media Relations
(404) 639-3286

April 1, 2024—A person in the United States has tested positive for highly pathogenic avian influenza (HPAI) A(H5N1) virus ("H5N1 bird flu"), as reported by Texas and confirmed by CDC. This person had exposure to dairy cattle in Texas presumed to be infected with HPAI A(H5N1) viruses. The patient reported eye redness (consistent with conjunctivitis), as their only symptom, and is recovering. The patient was told to isolate and is being treated with an antiviral drug for flu. This infection does not change the H5N1 bird flu human health risk assessment for the U.S. general public, which CDC considers to be low. However, people with close or prolonged, unprotected exposures to infected birds or other animals (including livestock), or to environments contaminated by infected birds or other animals, are at greater risk of infection. CDC has interim recommendations for prevention, monitoring, and public health investigations of HPAI A(H5N1) viruses.

CDC is working with state health departments to continue to monitor workers who may have been in contact with infected or potentially infected birds/animals and test those people who develop symptoms. CDC also has

What happened now

- Prior to this most cases, bird to human

Current Situation

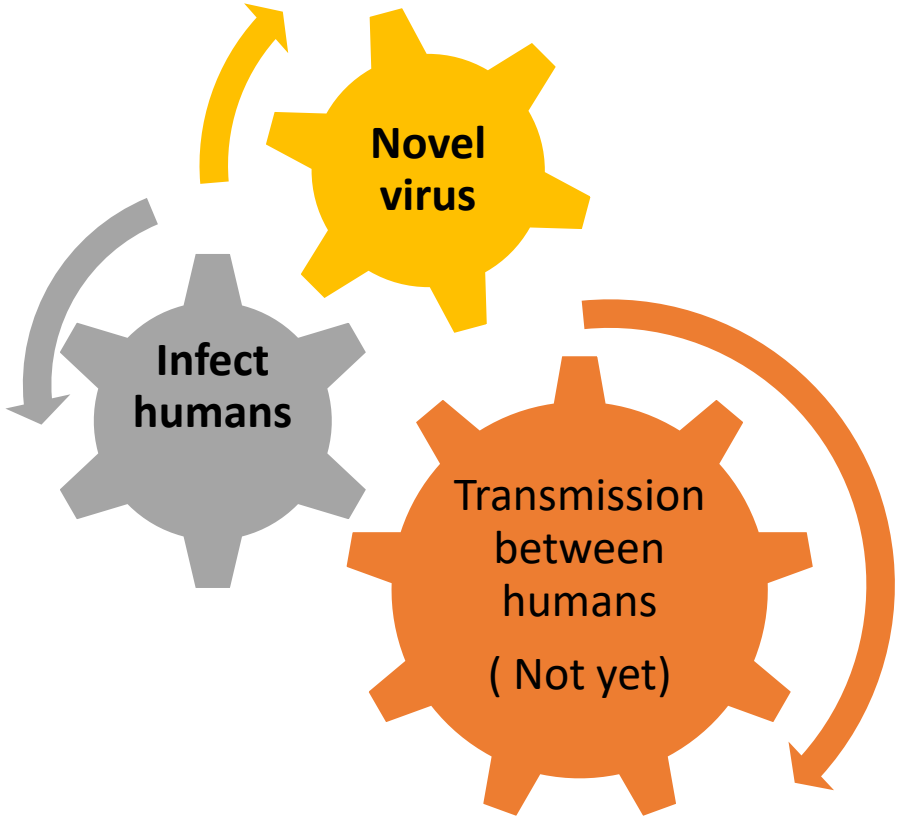
- Previously bovid animals weren't thought to play a role
- Prior transmissions in Hong Kong, Indonesia, China were from birds to humans
- This is a significant change and a potential step towards more widespread transmission?
- Need population level serologic data to determine if silent spillovers have happened

Current Situation

- Wastewater testing
- Have to be careful -> mixing of sewage from cattle farm runoffs and human waste
- Doesn’t mean it’s a foodborne illness

(milk)

The pandemic puzzle



Clinical illness

- Incubation (2-5 days, upto 7)
- URI symptoms with rapid progression to pneumonia and ARDS
- CFR → upto 50%, mostly young individuals
- (not a true reflection)
- For cattle, mild illness
- Most birds --> GI illness

Impact of Influenza Illness

- Death → most severe and devastating outcome (novel viruses)
- Economic impacts (lost work days, missed schools)
- For H5N1 all control measures focused on culling of millions of animals
- Severe economic impacts --> decreased egg and milk production

Case Reports > J Med Virol. 2001 Mar;63(3):242-6.
doi: 10.1002/1096-9071(200103)63:3<242::aid-jmv1007>3.0.co;2-n.

Pathology of fatal human infection associated with avian influenza A H5N1 virus

K F To [1], P K Chan, K F Chan, W K Lee, W Y Lam, K F Wong, N L Tang, D N Tsang, R Y Sung, T A Buckley, J S Tam, A F Cheng

Affiliations + expand

PMID: 11170064 DOI: 10.1002/1096-9071(200103)63:3<242::aid-jmv1007>3.0.co;2-n

Abstract

Eighteen cases of human influenza A H5N1 infection were identified in Hong Kong from May to December 1997. Two of the six fatal cases had undergone a full post-mortem which showed reactive hemophagocytic syndrome as the most prominent feature. Other findings included organizing diffuse alveolar damage with interstitial fibrosis, extensive hepatic central lobular necrosis, acute renal tubular necrosis and lymphoid depletion. Elevation of soluble interleukin-2 receptor, interleukin-6 and interferon-gamma was demonstrated in both patients, whereas secondary bacterial pneumonia was not observed. Virus detection using isolation, reverse transcription-polymerase chain reaction and immunostaining were all negative. It is postulated that in fatal human infections with this avian subtype, initial virus replication in the respiratory tract triggers hypercytokinemia complicated by the reactive hemophagocytic syndrome. These findings suggest that the pathogenesis of influenza A H5N1 infection might be different from that of the usual human subtypes H1-H3.

Cumulative number of confirmed human cases† for avian influenza A(H5N1) reported to WHO, 2003-2024

Country	2003-2009*		2010-2014*		2015-2019*		2020		2021		2022		2023		2024		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	0	0	0	0	0	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	0	0	0	0	6	4	5	1	67	42
Canada	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Chile	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
China	38	25	9	5	6	1	0	0	0	0	1	1	1	0	0	0	55	32
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Ecuador	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Egypt	90	27	120	50	149	43	0	0	0	0	0	0	0	0	0	0	359	120
India	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1
Indonesia	162	134	35	31	3	3	0	0	0	0	0	0	0	0	0	0	200	168
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nepal	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1
Spain	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2	0
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	4
United Kingdom	0	0	0	0	0	0	0	0	1	0	0	0	4	0	0	0	5	0
United States of America	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Viet Nam	112	57	15	7	0	0	0	0	0	0	1	0	0	0	1	1	129	65
Total	**468**	**282**	**233**	**125**	**160**	**48**	**1**	**0**	**2**	**1**	**6**	**1**	**12**	**4**	**6**	**2**	**888**	**463**

*2003-2009, 2010-2014 and 2015-2019 total figures. Breakdowns by year available on subsequent tables.
†This count includes reported detections in asymptomatic individuals. In some cases, the confirmation of infection versus transient contamination of the nasopharynx/oropharynx with virus particles after exposure to infected birds or contaminated environment remains inconclusive. Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases. All dates refer to onset of illness.
Source: WHO/GIP, data in HQ as of 28 March 2024.

World Health Organization

Treatment

- Supportive care mostly mild illness
- Secondary bacterial infections
- Oseltamavir, baloxavir, zanamivir

H5N1 Vaccines

AUDENZ

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STN: 125692
Proper Name: Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
Tradename: AUDENZ
Manufacturer: Seqirus, Inc.
Indication:

- AUDENZ is an inactivated vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine.
- AUDENZ is approved for use in persons 6 months of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Content current as of:
04/25/2024

Product Information

- Package Insert - AUDENZ
- Demographic Subgroup Information - AUDENZ
  Refer to Section 1.1 of the Clinical Review Memo for information about participation in the clinical trials and any analysis of demographic subgroup outcomes that is notable.

Oh what's the fuss then, there are vaccines!

- Mass production
- Rollout and allocation
- We know from COVID-19, its anything but smooth and equitable.
- All the while mutations and adaptation ongoing

April 5, 2024

MEMORANDUM

TO: **Vice Presidents, Clinical**
Ontario Health

FROM: **Dr. Kieran Moore,**
Chief Medical Officer of Health

RE: **Avian Influenza Surveillance in Hospitalized Patients**

Dear colleagues,

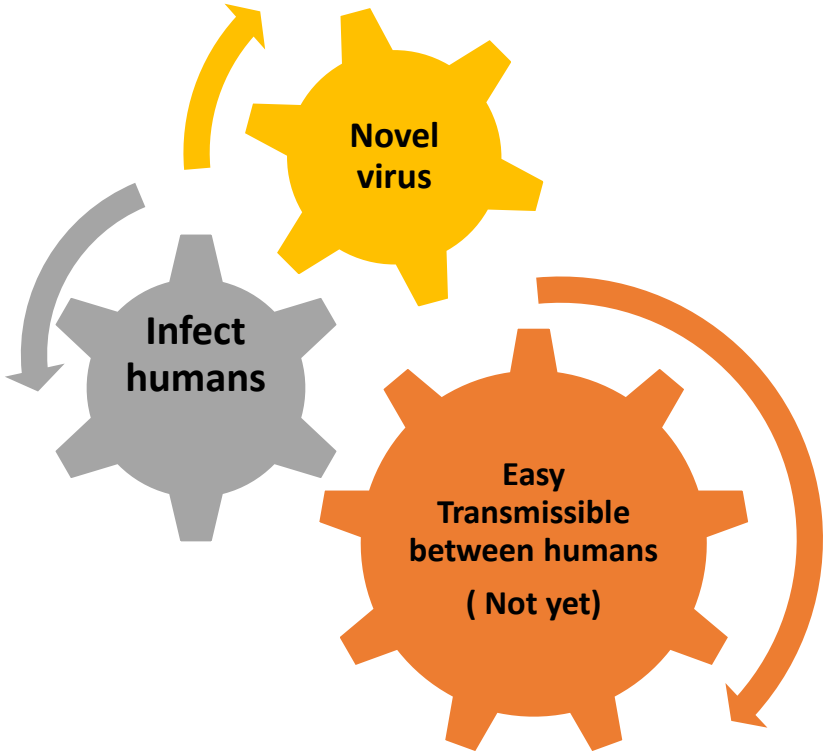
Highly pathogenic avian influenza (HPAI) H5N1 continues to circulate in Canada and internationally among domestic and wild birds, as well as detections in wild and domestic mammals that have had exposure to infected birds, including domestic cats and dogs.

Recently, HPAI has also been detected for the first time among livestock, including goats and cattle. In dairy cattle herds, infection has resulted in illness and decreased milk production. HPAI has also been detected in unpasteurized milk from

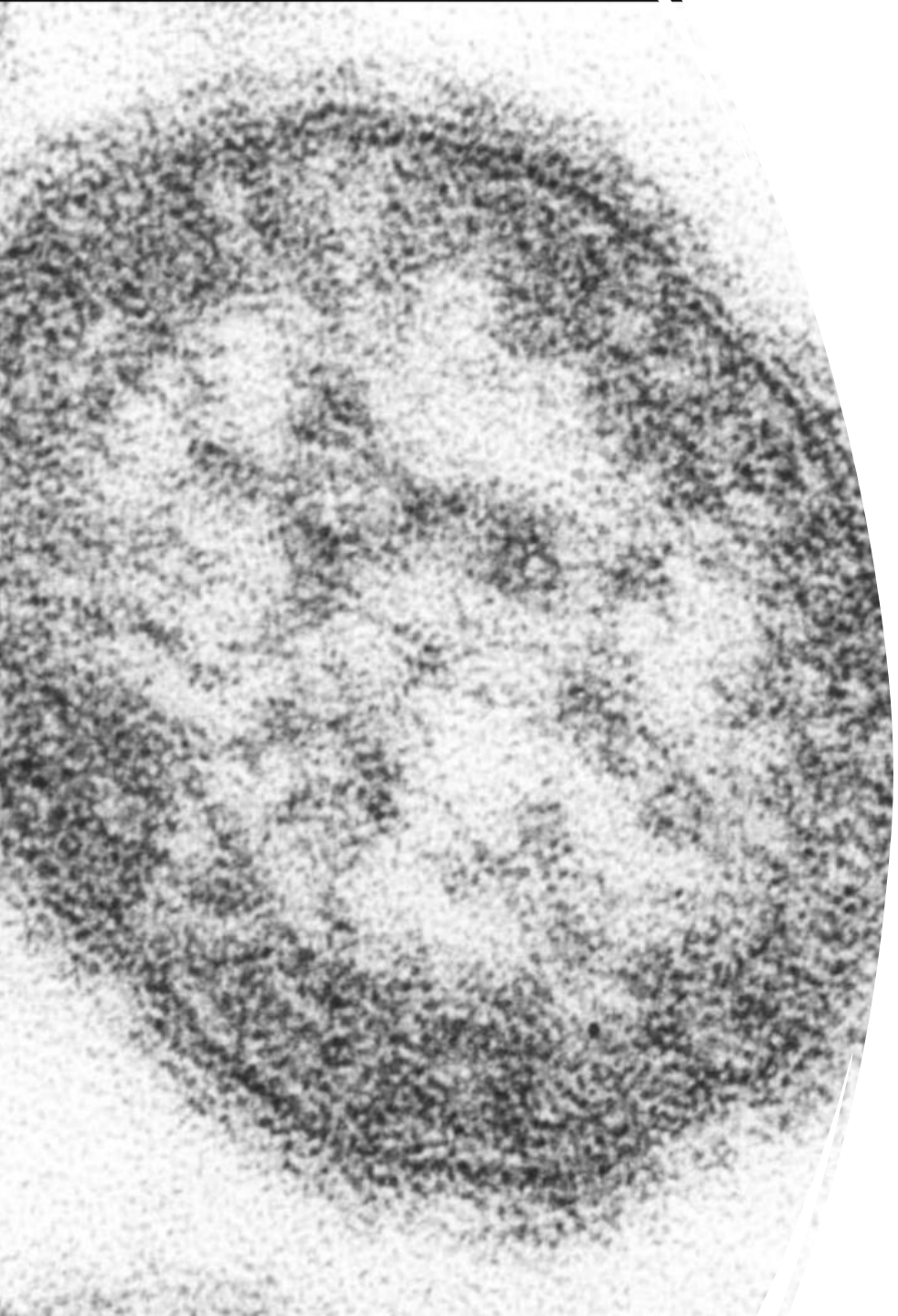
- **Screening of hospitalized patients:** Obtain a history from individuals with severe influenza/influenza-like symptoms regarding **potential exposures to infected birds or mammals, or to contaminated environmental surfaces**, **in the past 14 days prior to illness onset.**
  - This includes: occupational or recreational (e.g., hunting, hobby farms) close contact exposure to poultry, wild game, livestock, or other mammals; or consumption of raw/unpasteurized dairy products or undercooked meat from infected cattle.
  - If there is a relevant exposure history, notify your hospital infection prevention and control AND your local public health unit. Hospital infection prevention and control will advise further on necessary infection prevention and control precautions.
  - Further information for health professionals is available from the Public Health Agency of Canada.
  - Screening of all patients with influenza/influenza-like symptoms in the community or Emergency Department is NOT recommended due to the low risk to the public.

Bottomline

- Pandemic potential (novel virus + can infect humans)
- The risk assessment from PHAC is low for general population
- But there has been no widespread testing of cattle here
- The key is early identification



Measles, a re-emerging threat



Measles

- Highly infectious acute viral illness
- Measles has been described going back to 2,000 years (not novel)
- Virus identified in 1954
- Humans are only known reservoir (elimination is achievable and done)

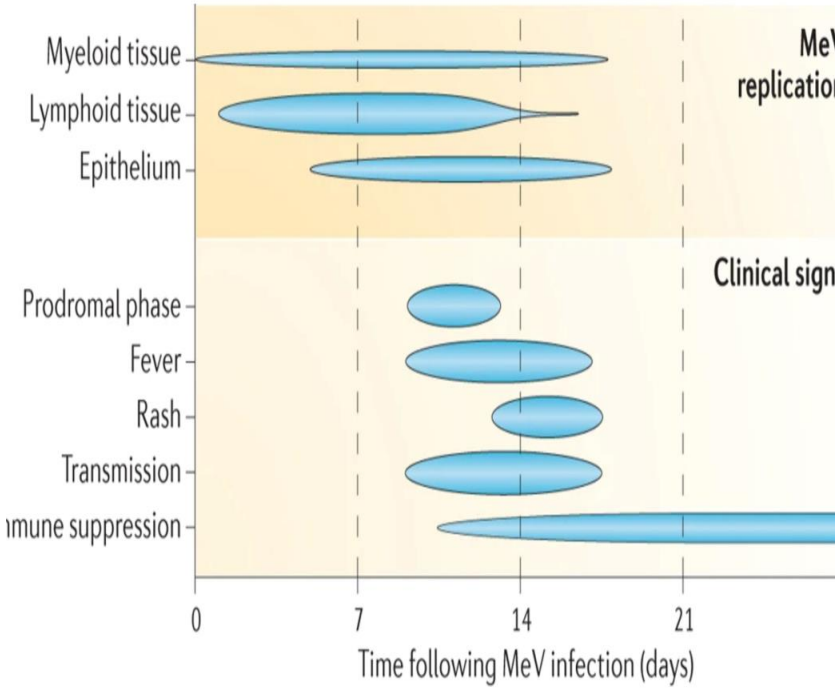
One of the most infectious viruses

- Transmitted via infectious aerosols (predominant) and respiratory droplets, as well as fomites
- Infectious particles can remain suspended for up to two (2) hours;
- 90% of non-immune people coming into contact with virus will develop the disease.
- SINGLE USE PPE

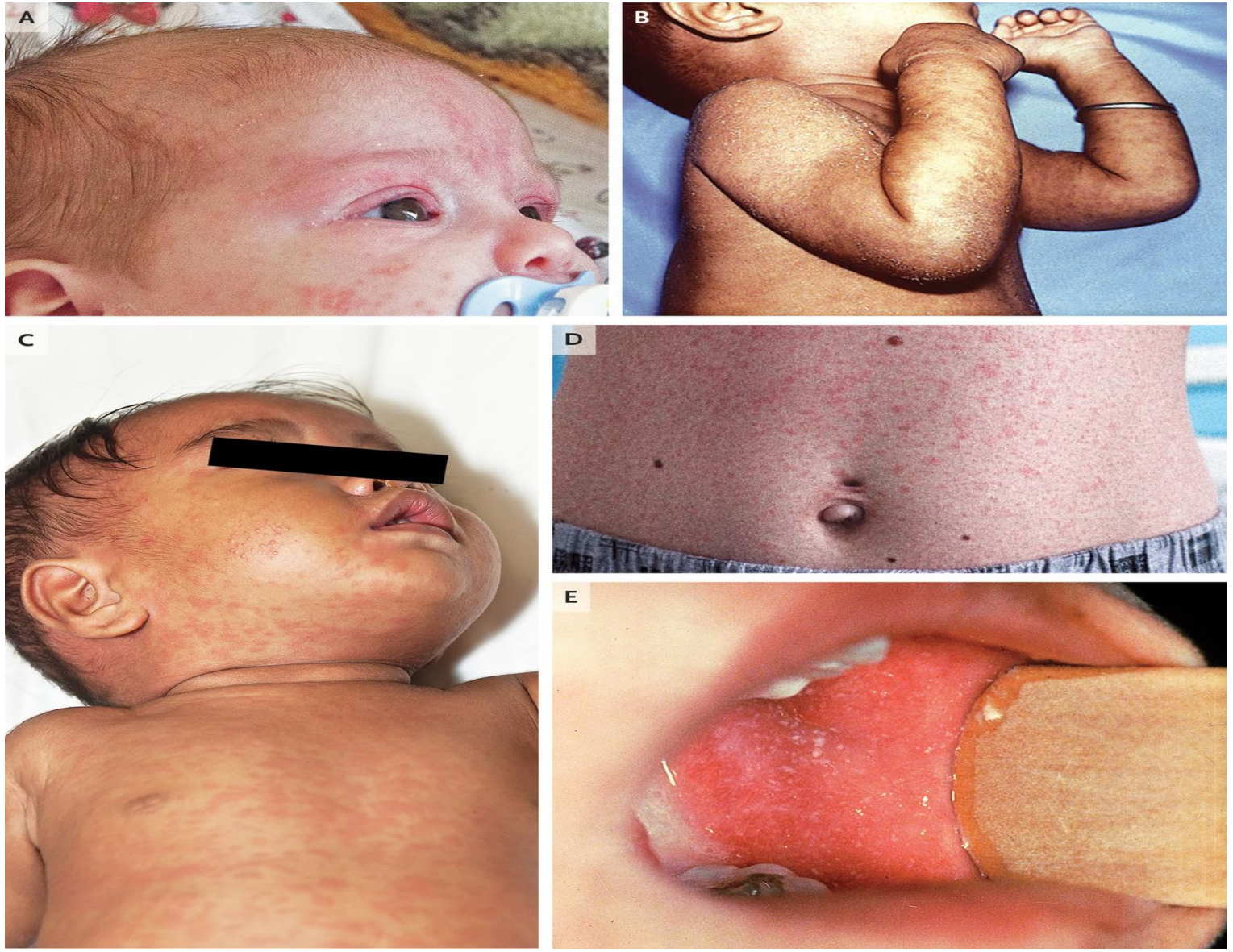
Measles the Disease

- Incubation period of 7-21 days
- Pro-dormal phase (Cough, conjunctivitis, coryza, “bad URI”)
- Koplik’s spots
- Measles rash

: Pathogenesis of measles.



Manifestations of Measles in Children



PM Strebel, WA Orenstein. N Engl J Med 2019;381:349-357.

Acute Measles Diagnosis

- Blood serology (IgG and IgM)
- Urine PCR test
- NP swab PCR test all sent at the same time
- If recent vaccination → **important to know as vaccine virus can be distinguished via PCR.**
- No Specific treatment

Complications

- **One out of every 1,000** measles cases will develop acute encephalitis, which often results in permanent brain damage.

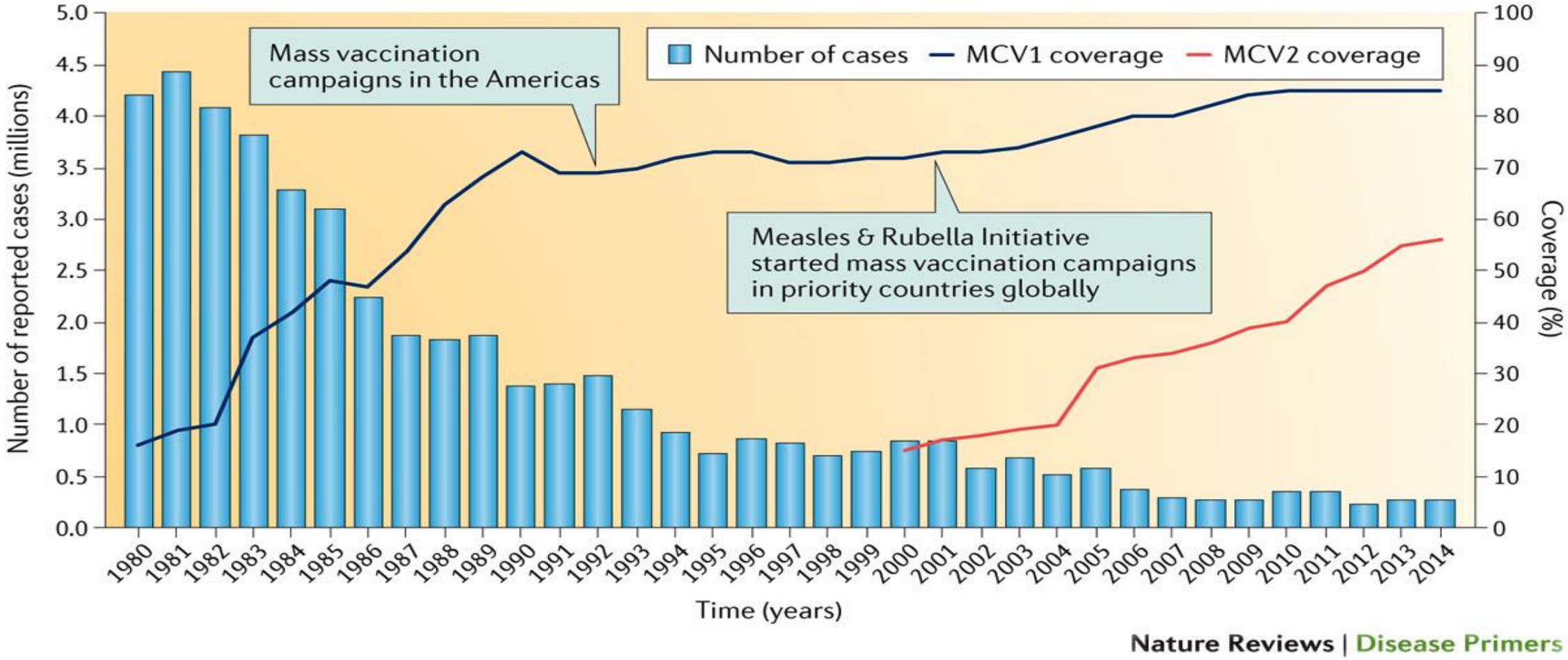
- **One to three out of every 1,000 children** who become infected with measles will die from respiratory and neurologic complications.

- Subacute sclerosing panencephalitis → rare, fatal degenerative disease of CNS, **seen 7-10 years** after infection

Epidemiology

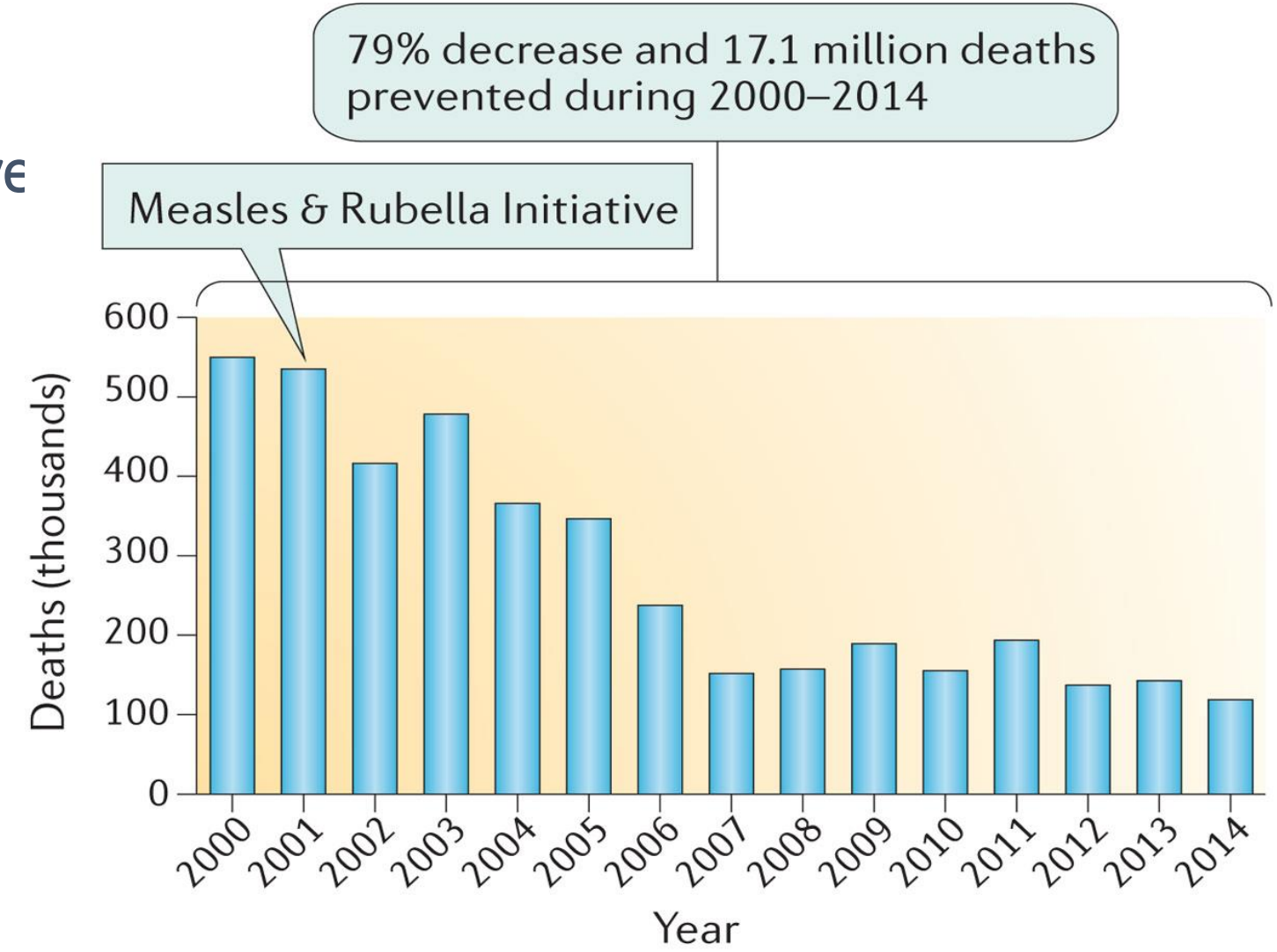
- Large scale outbreaks before effective measles vaccine became available in 1963
- Measles eliminated from Canada -> 1998;
- Tight balance of community immunity and transmissions locally (95% vaccination rates or higher)

Measles cases over time



Rota, P. A. *et al.* (2016) Measles
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.49

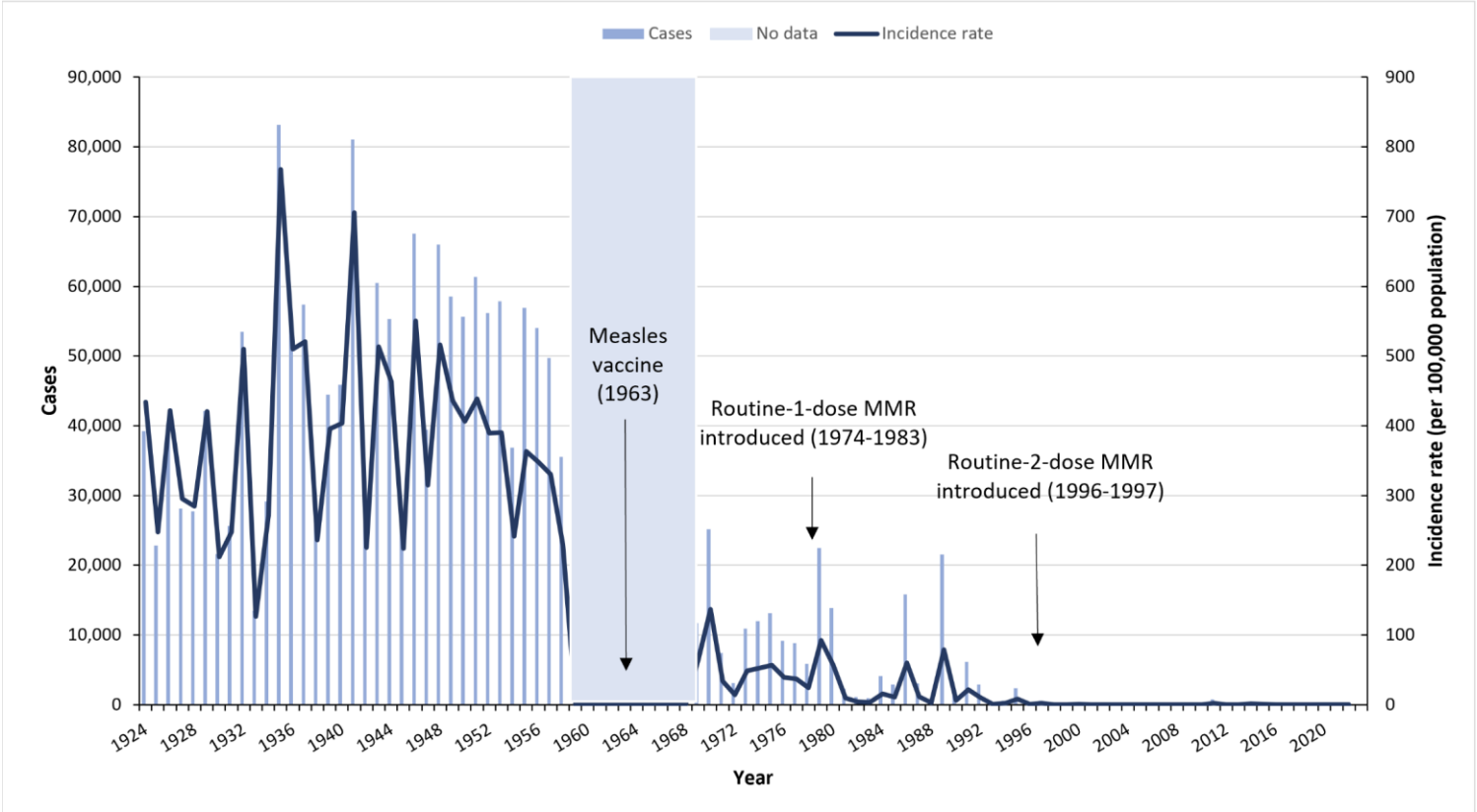
The number of estimated measles deaths globally by ye (2000–2014)



- Adapted with permission from Perry, R. *et al.* Progress toward regional measles elimination — worldwide, 2000–2014. *MMWR Morb. Mortal. Wkly Rep.* 64, 1246–1251 (2015), CDC

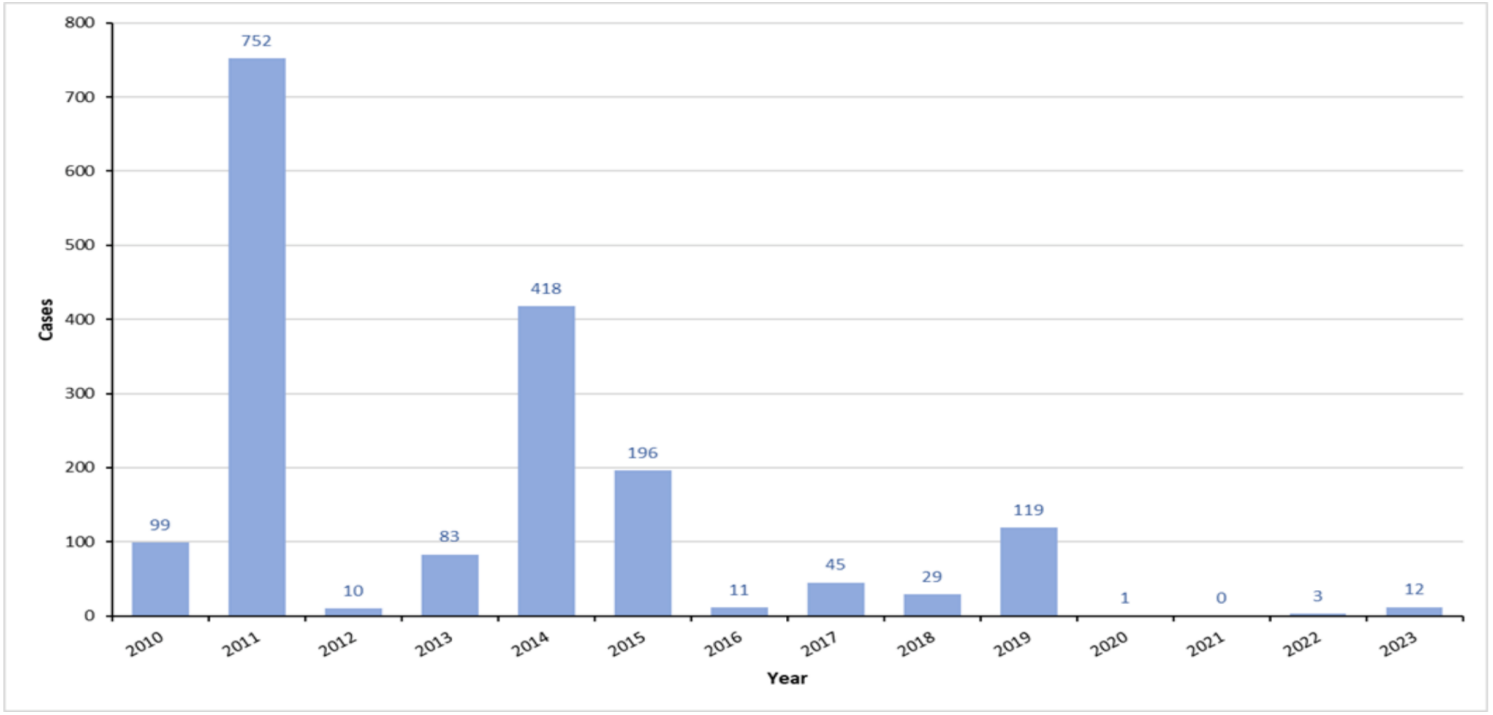
Measles in Canada

Figure 1. Number and incidence rates (per 100,000 population) of reported measles cases in Canada by year, 1924 to 2023



Measles in Canada

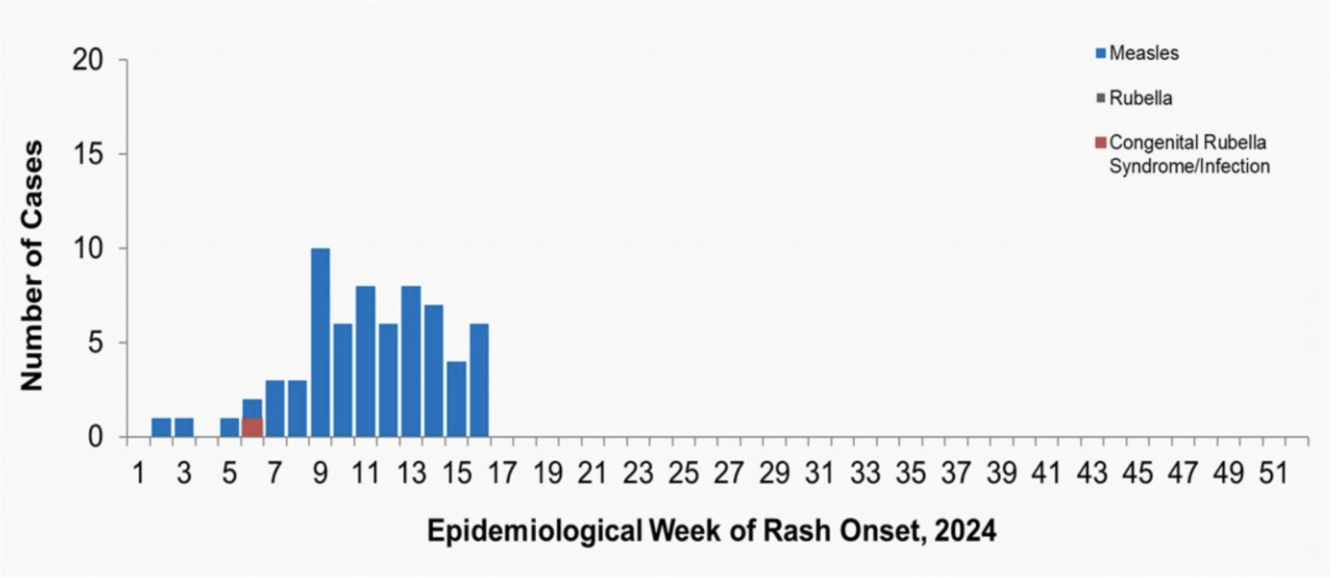
Figure 2. Number of reported measles cases in Canada by year, 2010-2023



Current Measles outbreak

To date in 2024, 65 cases of measles and 1 case of congenital rubella syndrome/infection have been reported. The last case of rubella was reported in September 2023.

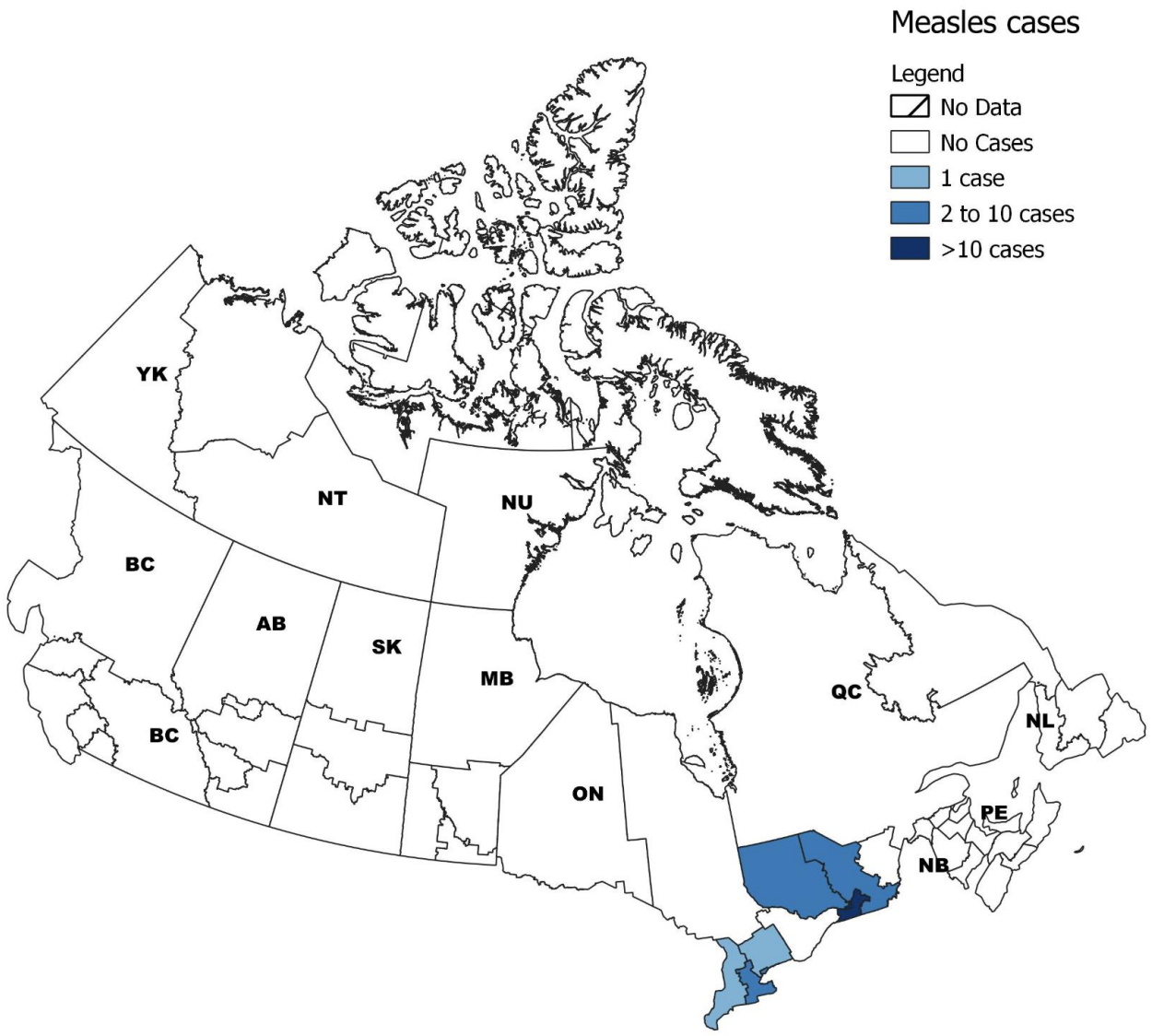
Figure 1: Number of cases of measles (n=65), rubella (n=0), and congenital rubella syndrome/infection (n=1) [3] by week of rash onset, as reported to the Canadian Measles/Rubella Surveillance System (CMRSS) and Measles and Rubella Surveillance System (MARS), for the period ending April 20, 2024.



▶ Figure 1 - Text description

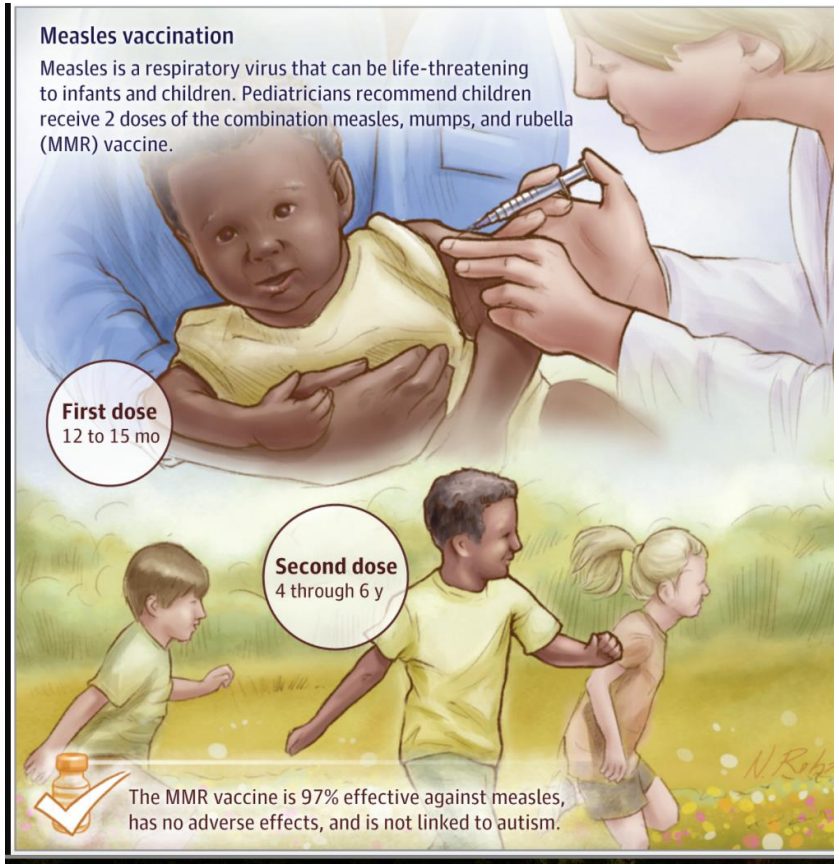
Geographic distribution

There are currently 45 active [*] cases of measles in Canada.

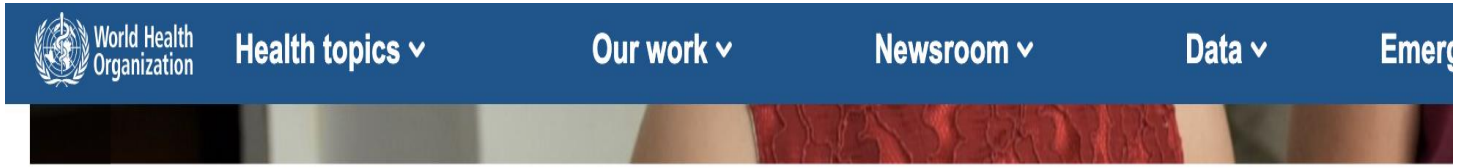

Measles cases
Legend
No Data
No Cases
1 case
2 to 10 cases
>10 cases
YK
NT
NU
BC
AB
SK
MB
ON
QC
NL
PE
NB
BC

Prevention

- Highly effective MMR vaccine
- Live attenuated vaccines (cannot give during pregnancy, immunosuppressed individuals)
- To be considered immune (infection, or **2 doses of vaccine** or serology)
- One dose: 93% effective
- Second dose 97% effective



What is happening now?



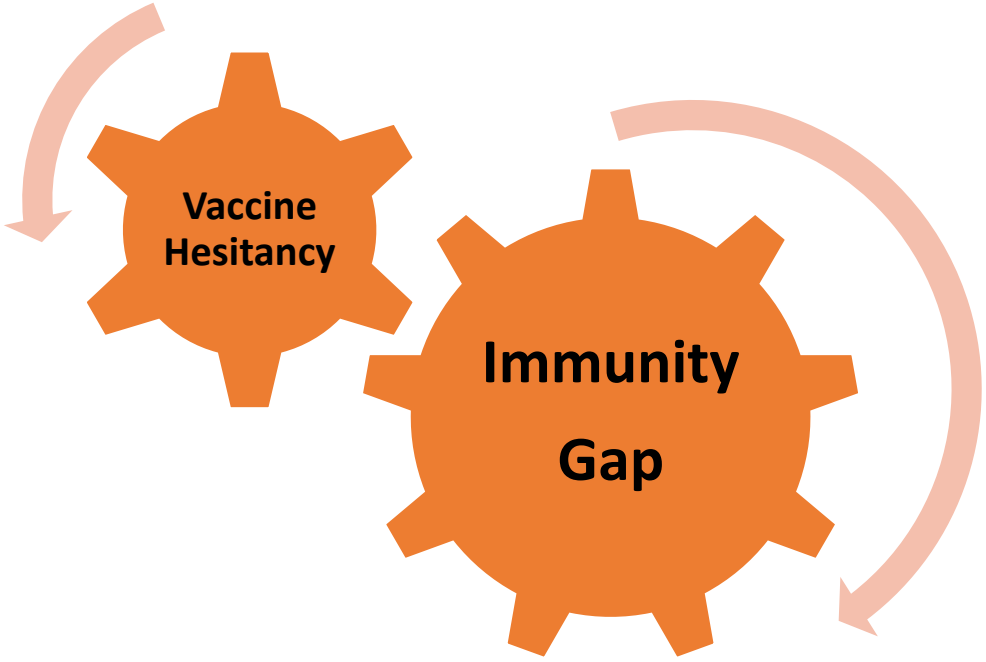
A 30-fold rise of measles cases in 2023 in the WHO European Region warrants urgent action

14 December 2023 | News release | Reading time: 2 min (675 words)

Prevention

- Vaccine is the biggest player in curtailing measles outbreaks
- MMR vaccine is one of the few vaccines that can be used as post exposure prophylaxis for ‘catch up’
- Exposed and susceptible individuals can receive measles immunoglobulin as well in **certain situations**
- Yes breakthrough infections occur but rare and mild

Why is this happening?



The Journal of Infectious Diseases

REVIEW

In Elimination Settings, Measles Antibodies Wane After Vaccination but Not After Infection: A Systematic Review and Meta-Analysis

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Steps to Take

Ensure everyone has had 2 doses of MMR vaccine

Or evidence of immunity

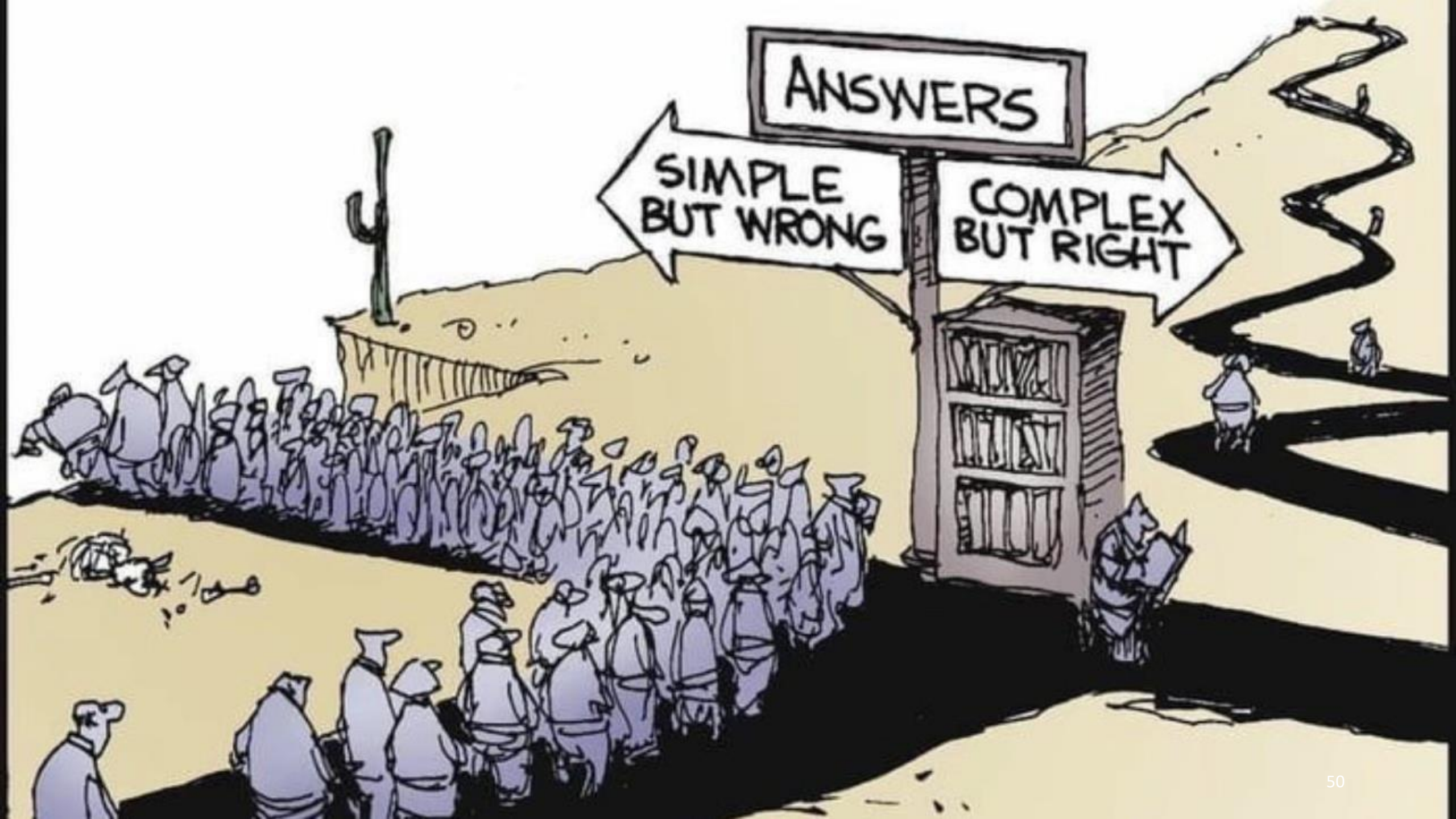
Be aware of alerts and exposure notices sent out by Public Health/ IPAC

Within hospital, connect immediately with your IPAC team member → even if patient not being admitted and just tested

Single use PPE

Fit tested seal checked N95 respirator with gowns, gloves and eye protection. PCRA


PUTTING IT ALL BEHIND US


ANSWERS
SIMPLE BUT WRONG
COMPLEX BUT RIGHT

Questions?

Masks under the chin, don’t protect anything!