Public Health Perspective: Federal Level

Andrew Beck, PhD

Centers for Disease Control and Prevention

Viral Vaccine Preventable Diseases Branch

Viral Classification Meeting

April 10, 2024

Disclaimer and Introduction

The findings and conclusions in this presentation are those of the author and not necessarily those of the Centers for Disease Control and Prevention.

Measles Classification is a Timely Issue

Notes from the Field

Measles Outbreak — Cook County, Illinois, October–November 2023

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On October 10, 2023, the Cook County Department of Public Health (CCDPH) in Illinois was notified by hospital A, a large pediatric facility, of a suspected measles case in a child aged 2 years (patient A) who had immigrated from Yemen on September 29 and who had no history of receipt of measles, mumps, and rubella (MMR) vaccine. The child visited hospital A's emergency department (ED) on October 5 with fever, cough, and coryza and, after receipt of negative COVID-19, influenza, and respiratory syncytial virus test results, received

Measles Classification is a Timely Issue

Morbidity and Mortality Weekly Report

Public Health Actions to Control Measles Among Afghan Evacuees During Operation Allies Welcome — United States, September–November 2021

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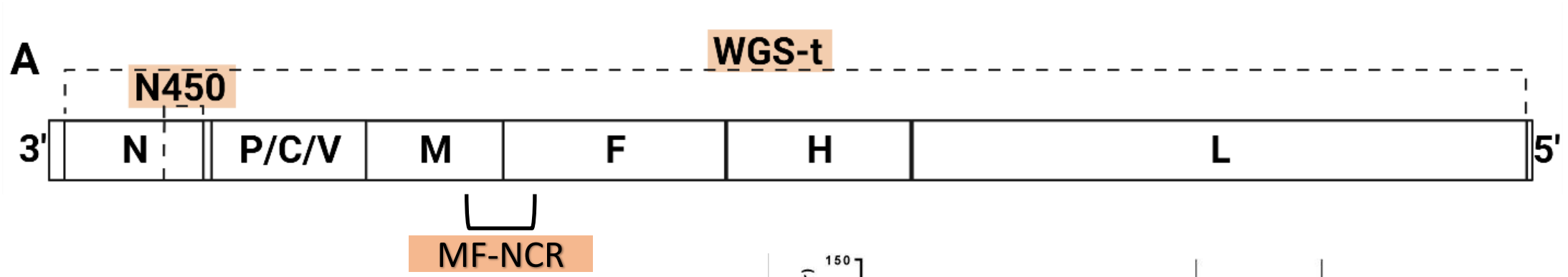
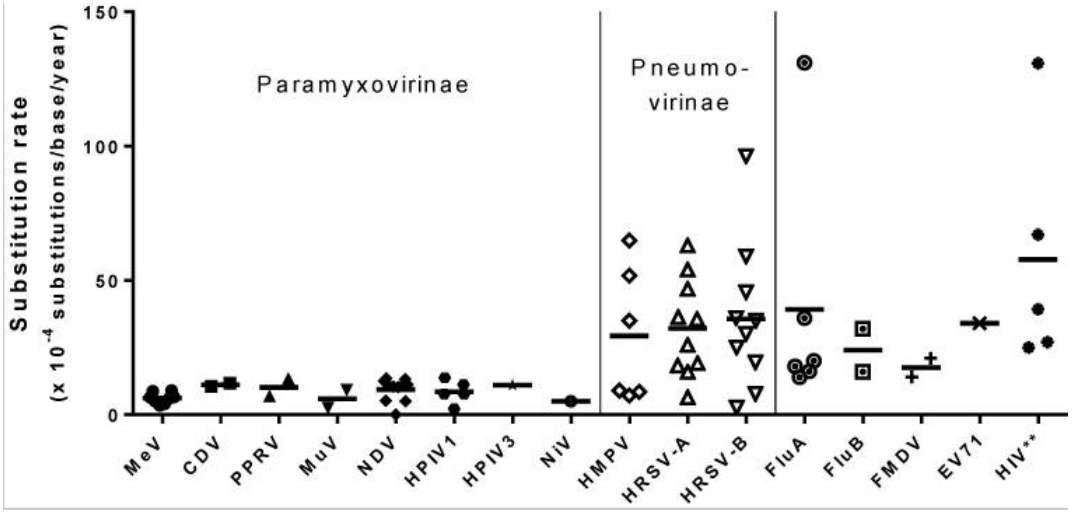
Measles Virus (MeV)

Restricted Diversity Landscape, Impact on Molecular Surveillance/Classification

MeV Genome Organization



- N450 is widely acquired for typing and molecular surveillance.
- Virus is monotypic (canonically).
- Low substitution rates



Current Typing

Molecular typing was proposed in 1996, based on nucleoprotein.

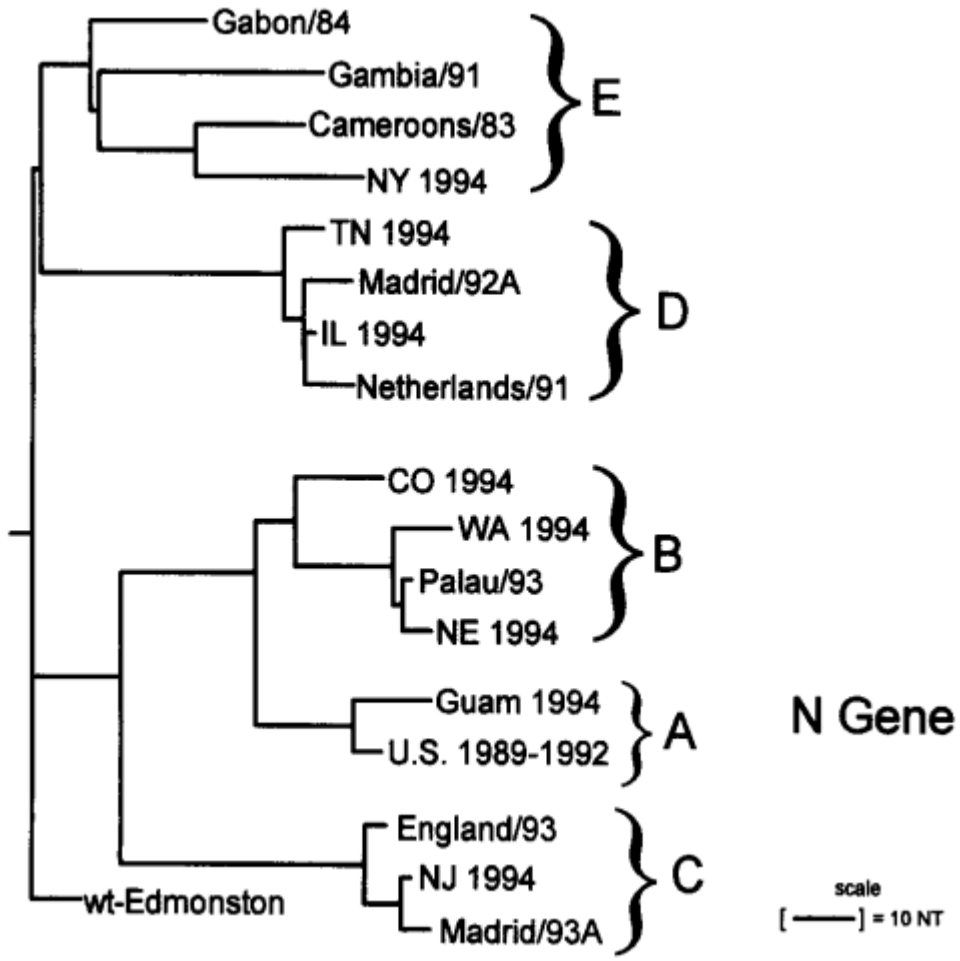
Current genotyping uses 8 clades (A-H), with numeric designation of genotype (24 described in total).

Standard sequences (N450 and H) are well-described and available.

Use of *named strains,* human-curated.

Use of *DSID* (distinct sequence ID).

N450 is universally collected into controlled surveillance network data.



Jennifer S. Rota, Janet L. Heath, Paul A. Rota, Gail E. King, María L. Celma, Juan Carabafia, Rafael Fernandez-Mũnoz, David Brown, Li Jin, William J. Bellini, Molecular Epidemiology of Measles Virus: Identification of Pathways of Transmission and Implications for Measles Elimination, *The Journal of Infectious Diseases*, Volume 173, Issue 1, January 1996, Pages 32–37, https://doi.org/10.1093/infdis/173.1.32

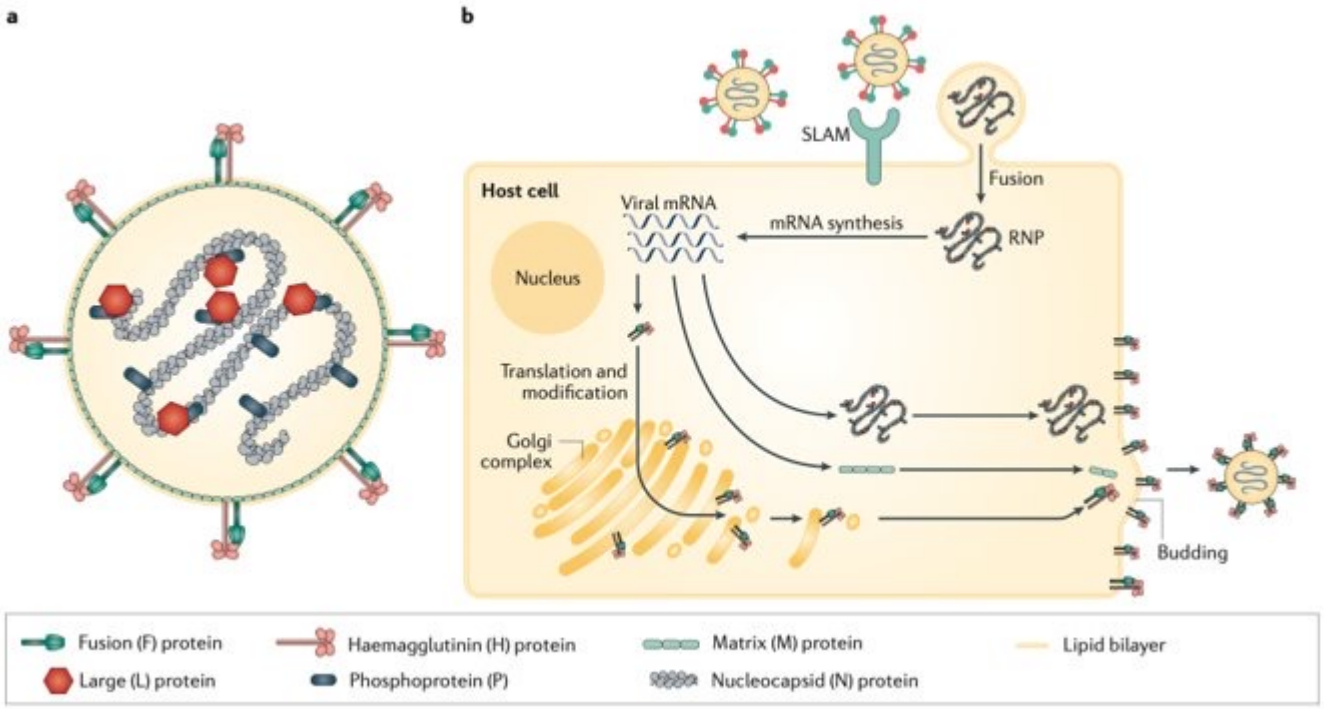
Current Nomenclature

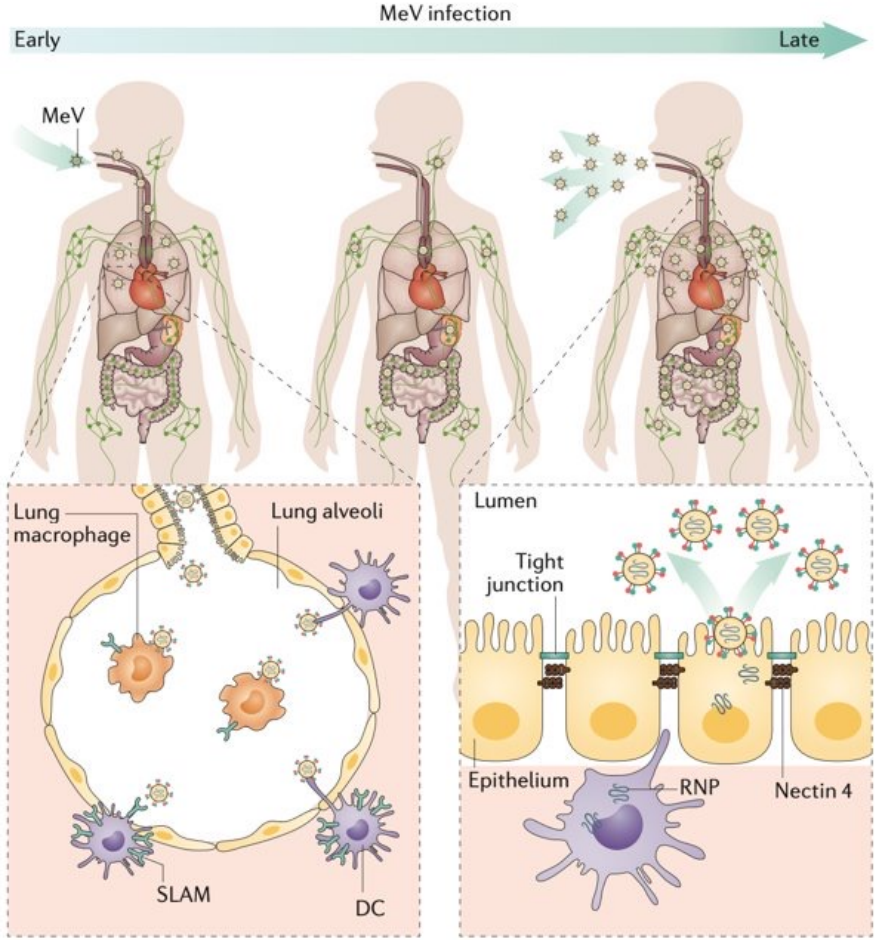
MVs/Maryland.USA/44.12/1[B3]

Other information that would be useful as sequences become less diverse:

- Lineage designation
- Relationship of sequence to others within a lineage
- Some representation of sequence identity

Pathogenesis: Restriction of Multiple Receptors



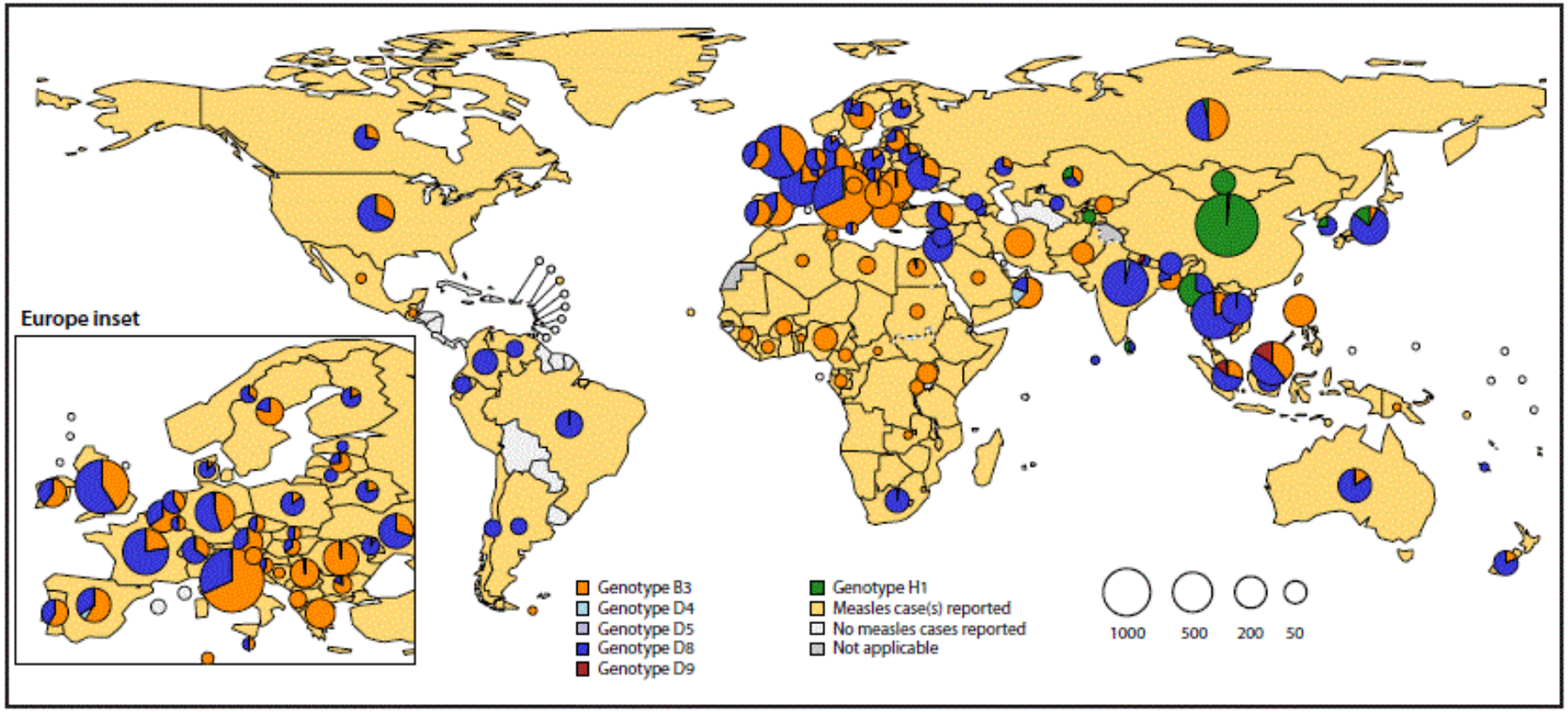


Lymphocyte (entry) – SLAM
Lung epithelium (exit) – Nectin 4

Rota, P., Moss, W., Takeda, M. *et al.* Measles. *Nat Rev Dis Primers* **2**, 16049 (2016). https://doi.org/10.1038/nrdp.2016.49

Epidemiology: Reduced Diversity of Circulating Types Over Time

FIGURE. Global distribution of measles virus genotypes,* 2016–2018



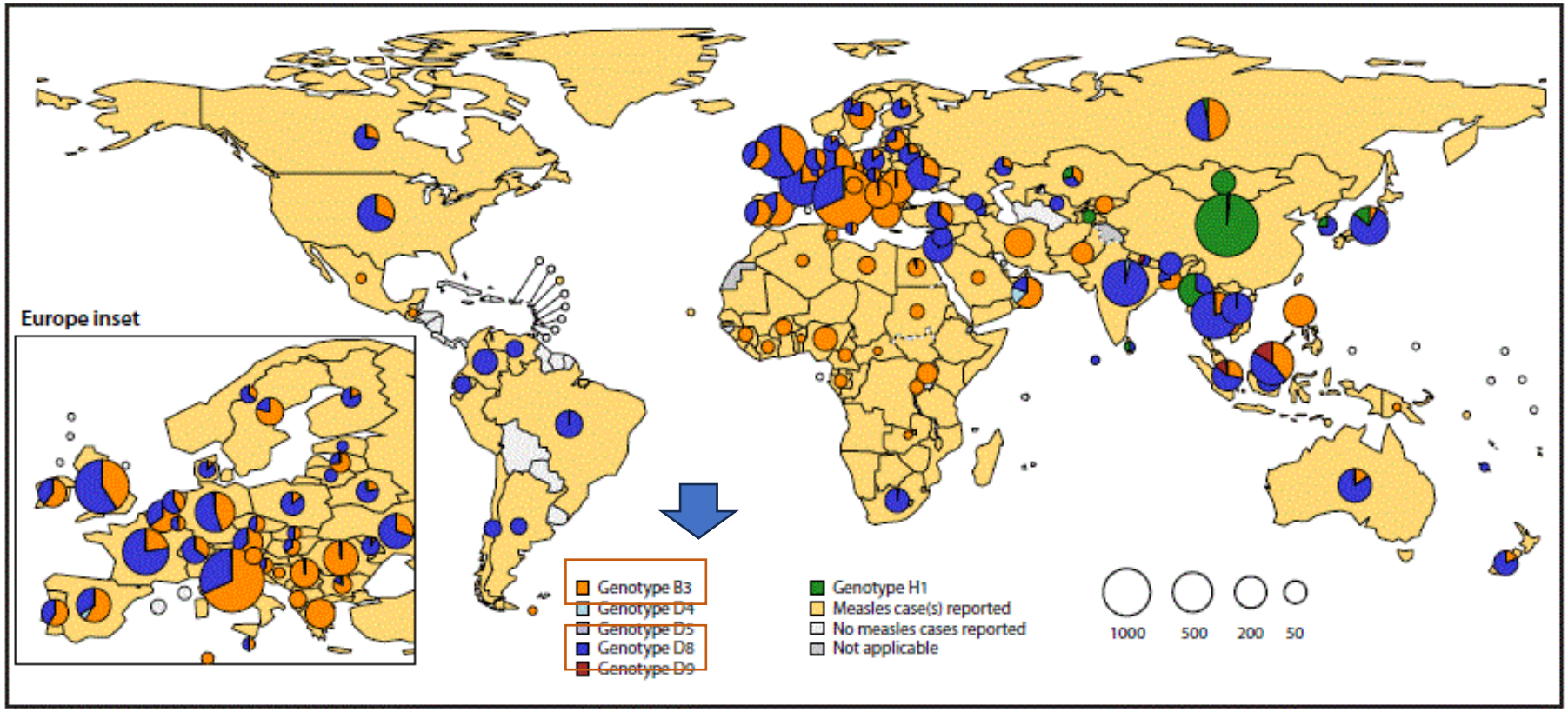
Source: World Health Organization.

* The size of the circles reflects the numbers of replicates reported for each genotype.

Brown KE, Rota PA, Goodson JL, Williams D, Abernathy E, Takeda M, Mulders MN. Genetic Characterization of Measles and Rubella Viruses Detected Through Global Measles and Rubella Elimination Surveillance, 2016-2018. MMWR Morb Mortal Wkly Rep. 2019 Jul 5;68(26):587-591.

Epidemiology: Reduced Diversity of Circulating Types Over Time

FIGURE. Global distribution of measles virus genotypes, Present Day



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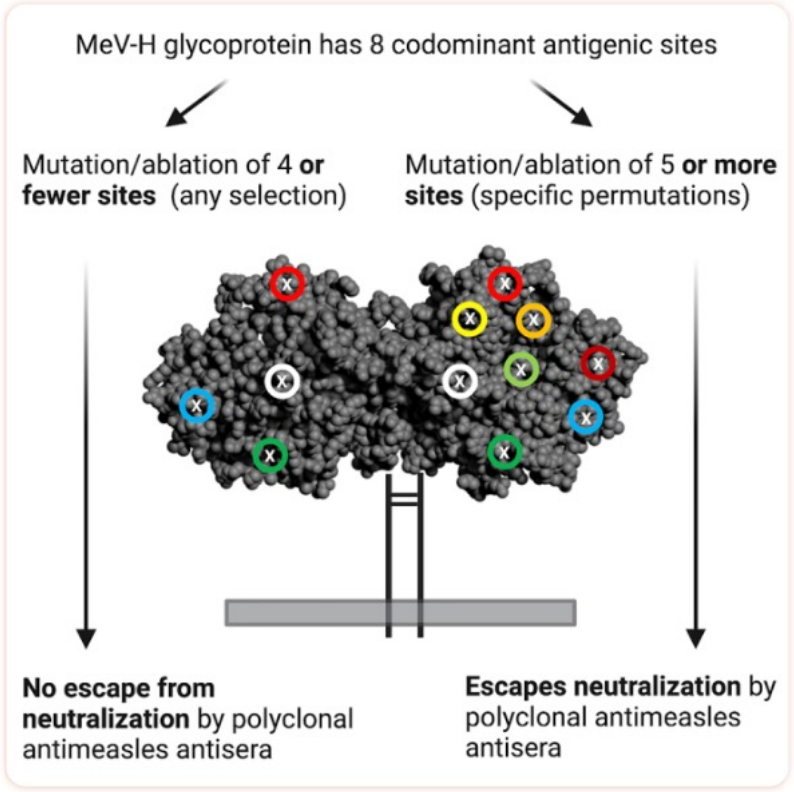
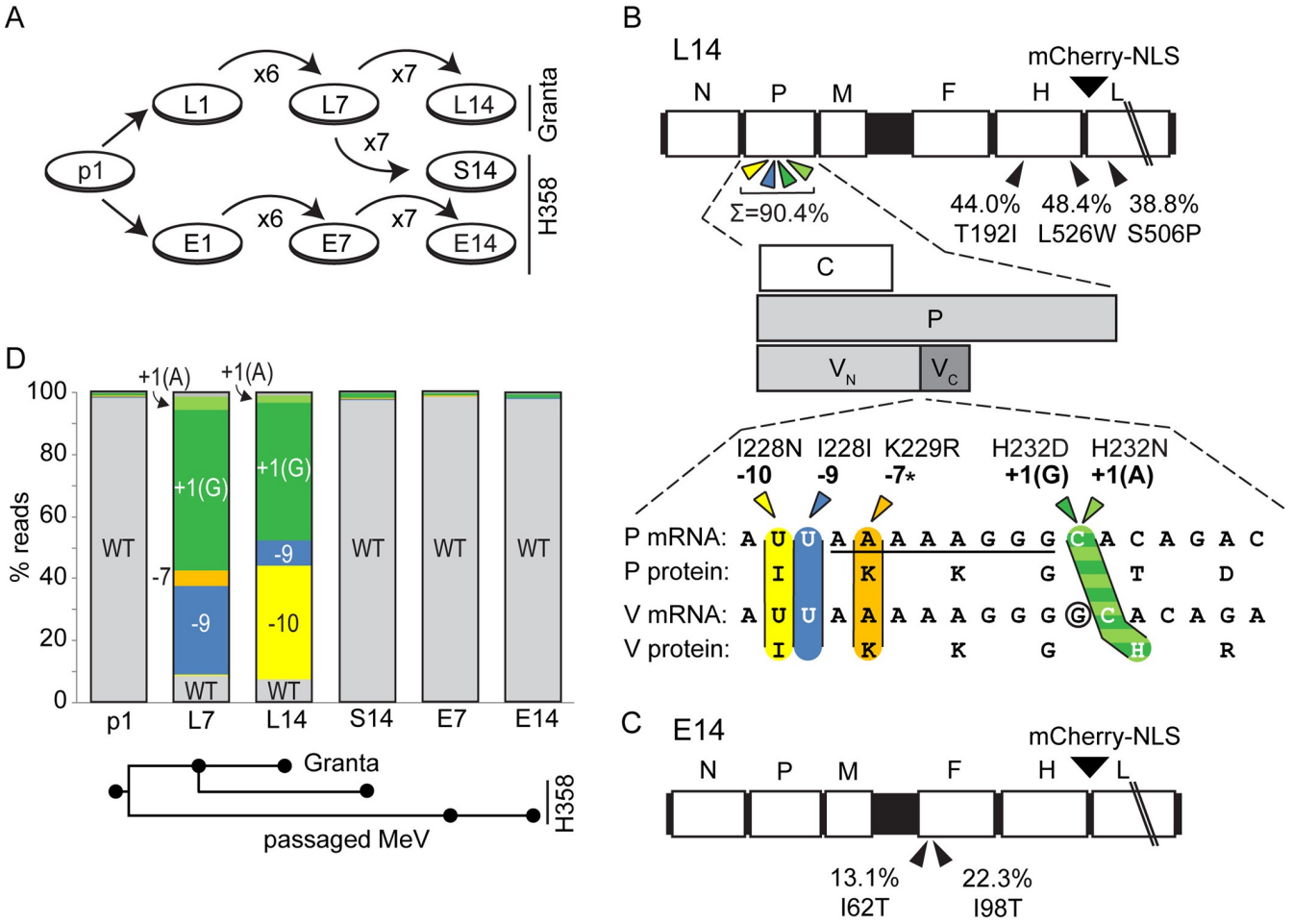
Quasispecies and Structural Constraints



Muñoz-Alía MÁ, Nace RA, Zhang L, Russell SJ. Serotypic evolution of measles virus is constrained by multiple co-dominant B cell epitopes on its surface glycoproteins. Cell Rep Med. 2021 Mar 30;2(4):100225. doi: 10.1016/j.xcrm.2021.100225.

Quasispecies and Structural Constraints



Granta: B-Lymphocyte (accumulates +G editing)

H358: Lung epithelial

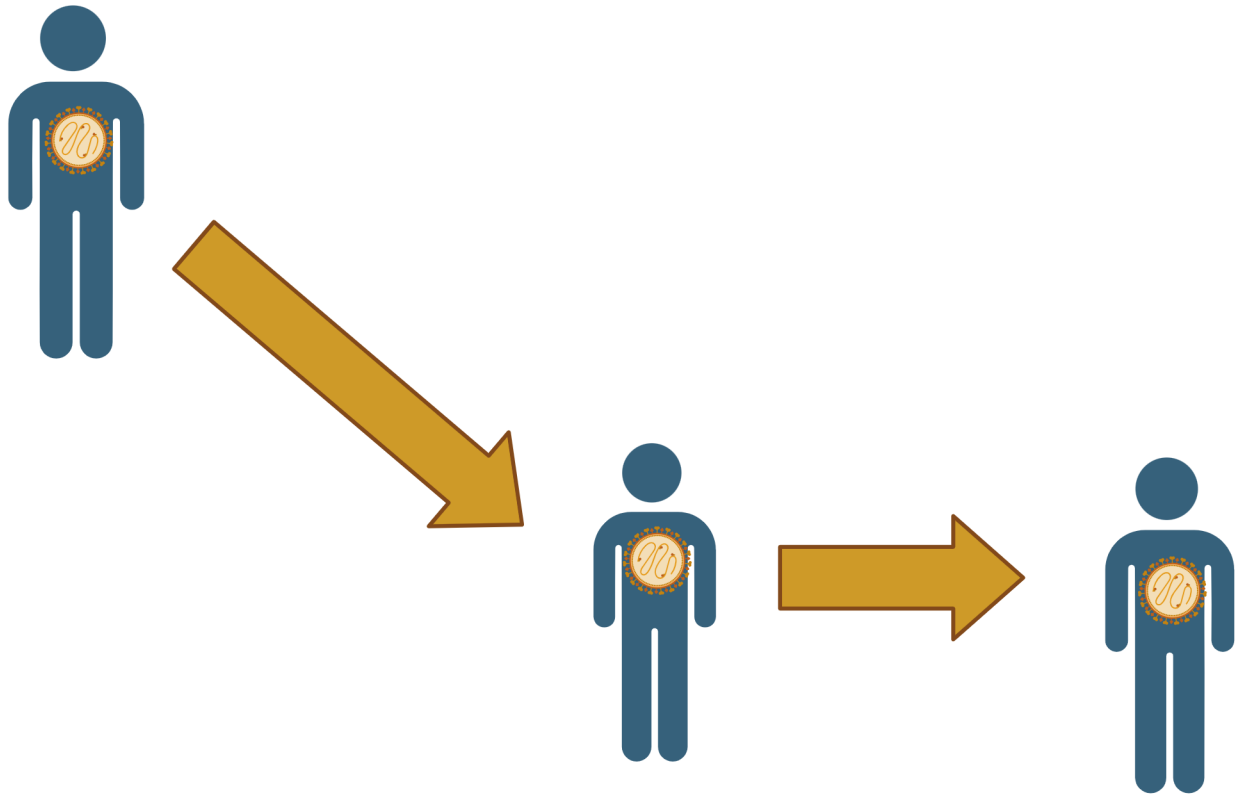
Donohue RC, Pfaller CK, Cattaneo R. Cyclical adaptation of measles virus quasispecies to epithelial and lymphocytic cells: To V, or not to V. PLoS Pathog. 2019 Feb 15;15(2):e1007605. doi: 10.1371/journal.ppat.1007605.

Elimination and Transmission Chain Discrimination

Measles elimination: The absence of endemic measles virus transmission in a defined geographical area (e.g. region or country) for at least 12 months in the presence of a surveillance system that has been verified to be performing well.

Chief Concern - Maintain elimination by tracking a virus that is:

(1) most contagious
(2) structurally constrained,
(3) genetically stable,
(4) in an environment of decreasing diversity of circulating sequences
(5) While using a large surveillance network with varying resources.



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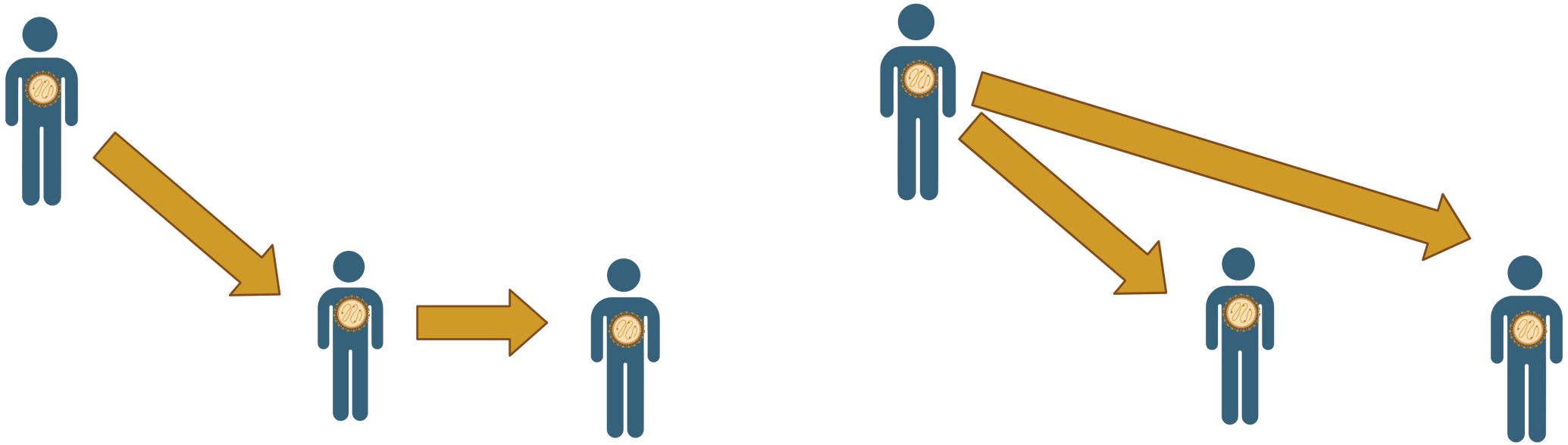
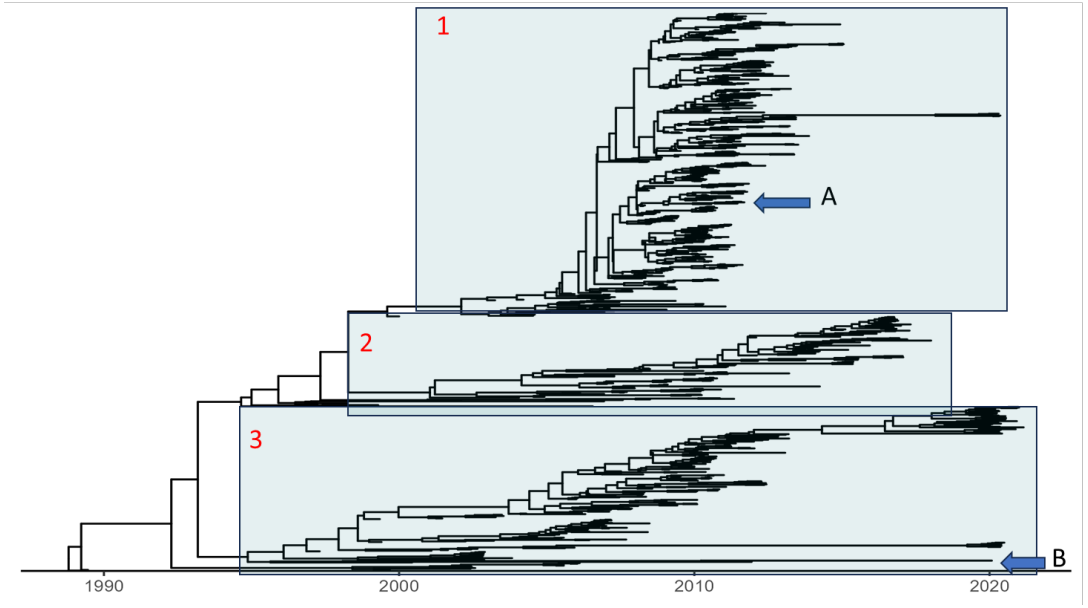
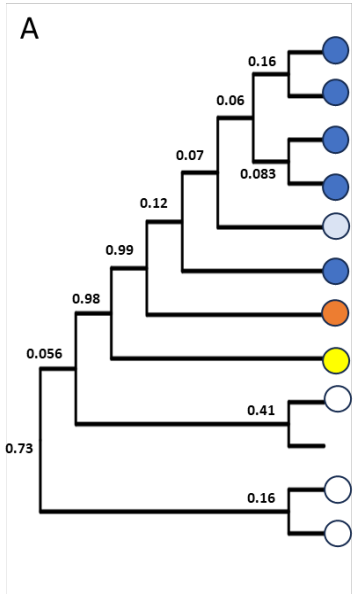
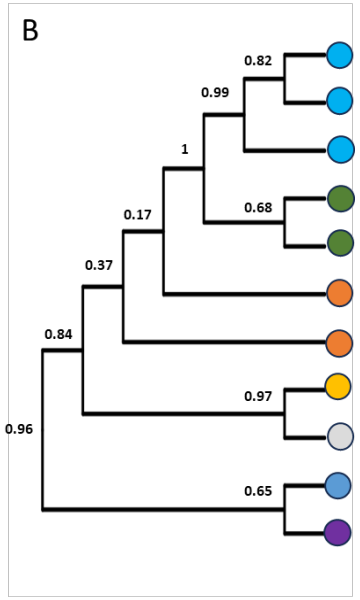


Genetic homogeneity: Overestimation of transmission chain length.

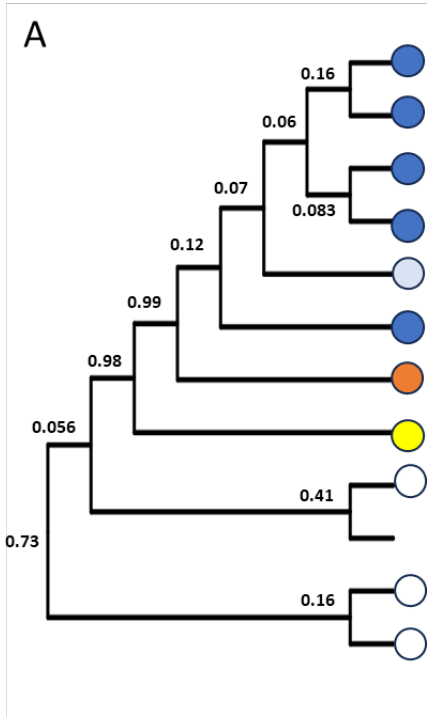
Multiple DSID Observed in Single Monophyletic Groups







Same color = Same DSID



MVs/Soltau.DEU/25.09
MVs/Rosenheim.DEU/18.09
MVs/Heidelberg.DEU/24.09
MVs/Aberdeen.GBR/11.09
MVs/Teeside.GBR/22.09
MVs/Birmingham.GBR/7.09
MVs/Guildford.GBR/14.09
MVs/Chester.GBR/38.08
MVs/Muenchen.DEU/18.09
MVs/Malaga.ESP/36.08
MVs/Truro.GBR/30.08

1. MeV genetic classification is in **transition**.
2. Using N450 molecular clocks, many well-supported groups contain multiple DSIDs [**colors**].
3. Geographic and time information is reasonable for some of these groups.

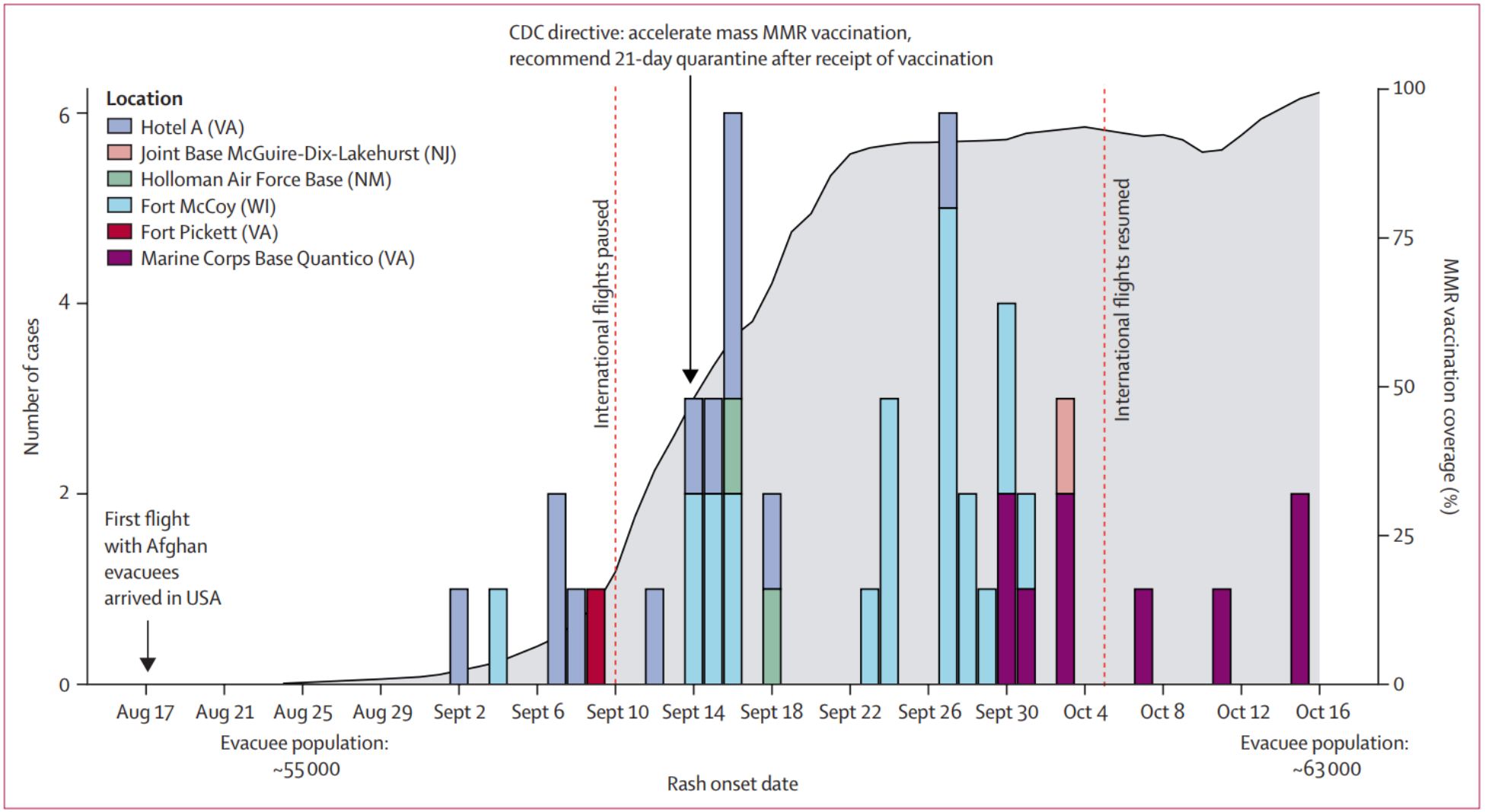
Hyun Hwang, Personal Communication

Integration of Sequence Data in Outbreak Response

Measles virus transmission patterns and public health responses during Operation Allies Welcome: a descriptive epidemiological study

Nina B Masters, Andrew S Beck, Adria D Mathis, Jessica Leung, Kelley Raines, Prabasaj Paul, Scott E Stanley, Alden L Weg, Emily G Pieracci, Shannon Gearhart, Madina Jumabaeva, Bettina Bankamp, Paul A Rota, David E Sugerman, Paul A Gastañaduy

Masters NB, Beck AS, Mathis AD, Leung J, Raines K, Paul P, Stanley SE, Weg AL, Pieracci EG, Gearhart S, Jumabaeva M, Bankamp B, Rota PA, Sugerman DE, Gastañaduy PA. Measles virus transmission patterns and public health responses during Operation Allies Welcome: a descriptive epidemiological study. Lancet Public Health. 2023 Aug;8(8):e618-e628. doi: 10.1016/S2468-2667(23)00130-5.



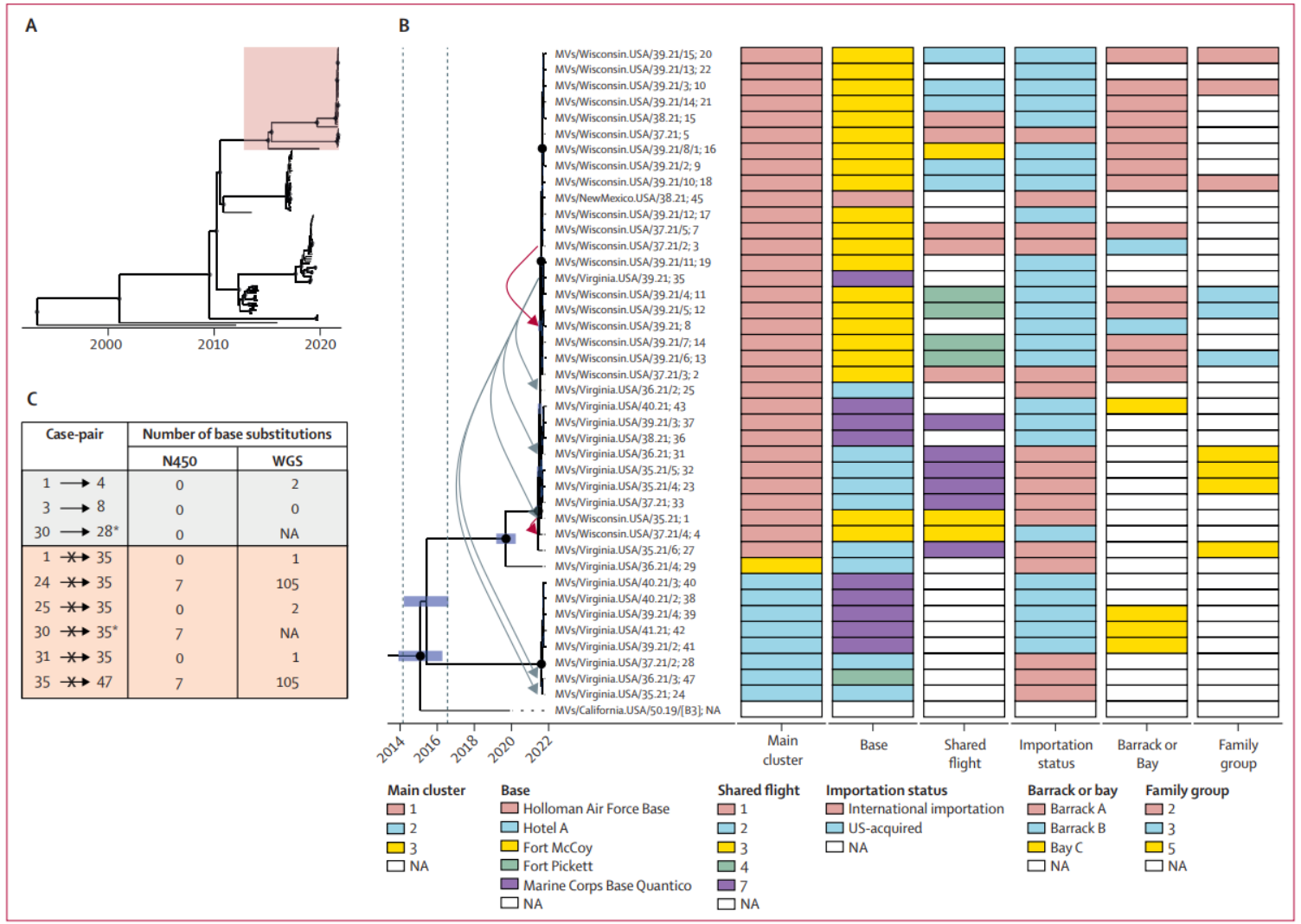
Masters NB, Beck AS, Mathis AD, Leung J, Raines K, Paul P, Stanley SE, Weg AL, Pieracci EG, Gearhart S, Jumabaeva M, Bankamp B, Rota PA, Sugerman DE, Gastañaduy PA. Measles virus transmission patterns and public health responses during Operation Allies Welcome: a descriptive epidemiological study. Lancet Public Health. 2023 Aug;8(8):e618-e628. doi: 10.1016/S2468-2667(23)00130-5.

WGS was acquired for 43 of 47 cases.

Pertinent variables are shown if available.

Red arrow: Plausible transmission pairs.

Limits of resolution in scenarios of complex importation from genetically similar sequences.



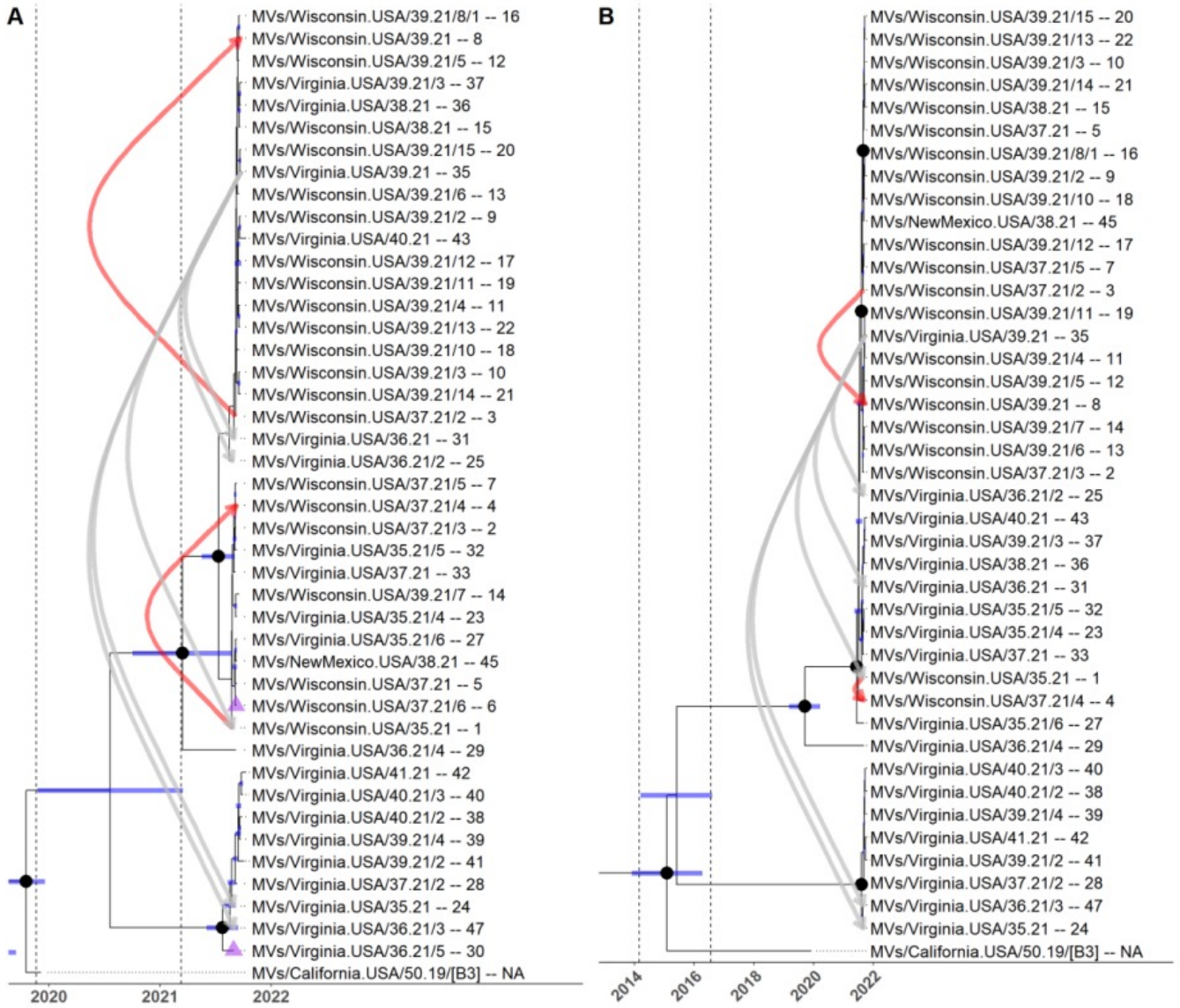
C

Case-pair	Number of base substitutions	
	N450	WGS
1 → 4	0	2
3 → 8	0	0
30 → 28*	0	NA
1 ↛ 35	0	1
24 ↛ 35	7	105
25 ↛ 35	0	2
30 ↛ 35*	7	NA
31 ↛ 35	0	1
35 ↛ 47	7	105

Masters NB, Beck AS, Mathis AD, Leung J, Raines K, Paul P, Stanley SE, Weg AL, Pieracci EG, Gearhart S, Jumabaeva M, Bankamp B, Rota PA, Sugerman DE, Gastañaduy PA. Measles virus transmission patterns and public health responses during Operation Allies Welcome: a descriptive epidemiological study. Lancet Public Health. 2023 Aug;8(8):e618-e628. doi: 10.1016/S2468-2667(23)00130-5.

Integration of Epidemiologic Linkage With Genetic Groupings

1. Geneticists and epidemiologists enter the same room and are forced to collectively interpret.
2. Payoff(s)
    1. Cross validation of datasets
    2. An (ultimately) more complete reconstruction of the infectious process.



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Revising MeV Classification for Elimination Contexts

What are the major needs?

Heuristics

We cannot ask most labs in surveillance networks to perform Bayesian analyses.

Base-tree assignment methods are actively being investigated.

Use of Sparse and Multifactor Data

Cases are missed, linkage is uncertain (sparse genetic or linkage).

Validated Software, Models and Parameters

Well-described behavior, well-tested, well-integrated, well-maintained.

Revisions of MeV nomenclature

Ongoing in our laboratory. Standard MeV data is heavily controlled and reliable.

This additional information should be ***epidemiologically meaningful to approximate transmission lineages*.**

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Hyun Hwang, BS
Cynthia Dixey, MS
CDC Office of Scientific Computing
CDC Office of Advanced Molecular Detection

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