Beth Israel Lahey Health
Mount Auburn Hospital

Harvard Medical School

Travel-Associated Influenza and COVID-19

Lin H. Chen, MD, FACP, FASTMH, FISTM
Director, Mount Auburn Travel Medicine Center
Associate Professor of Medicine, Harvard Medical School
Immediate Past President, International Society of Travel Medicine
ESWI 30 November, 2023

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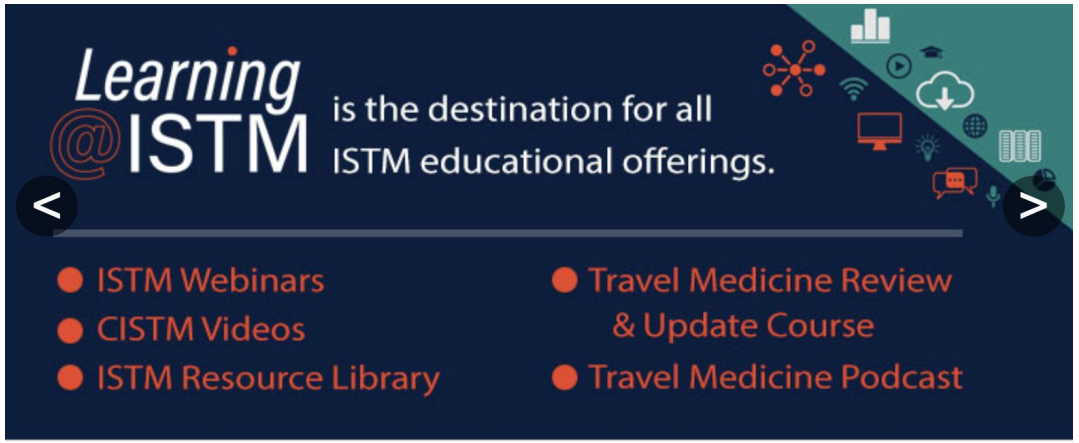


Disclosures

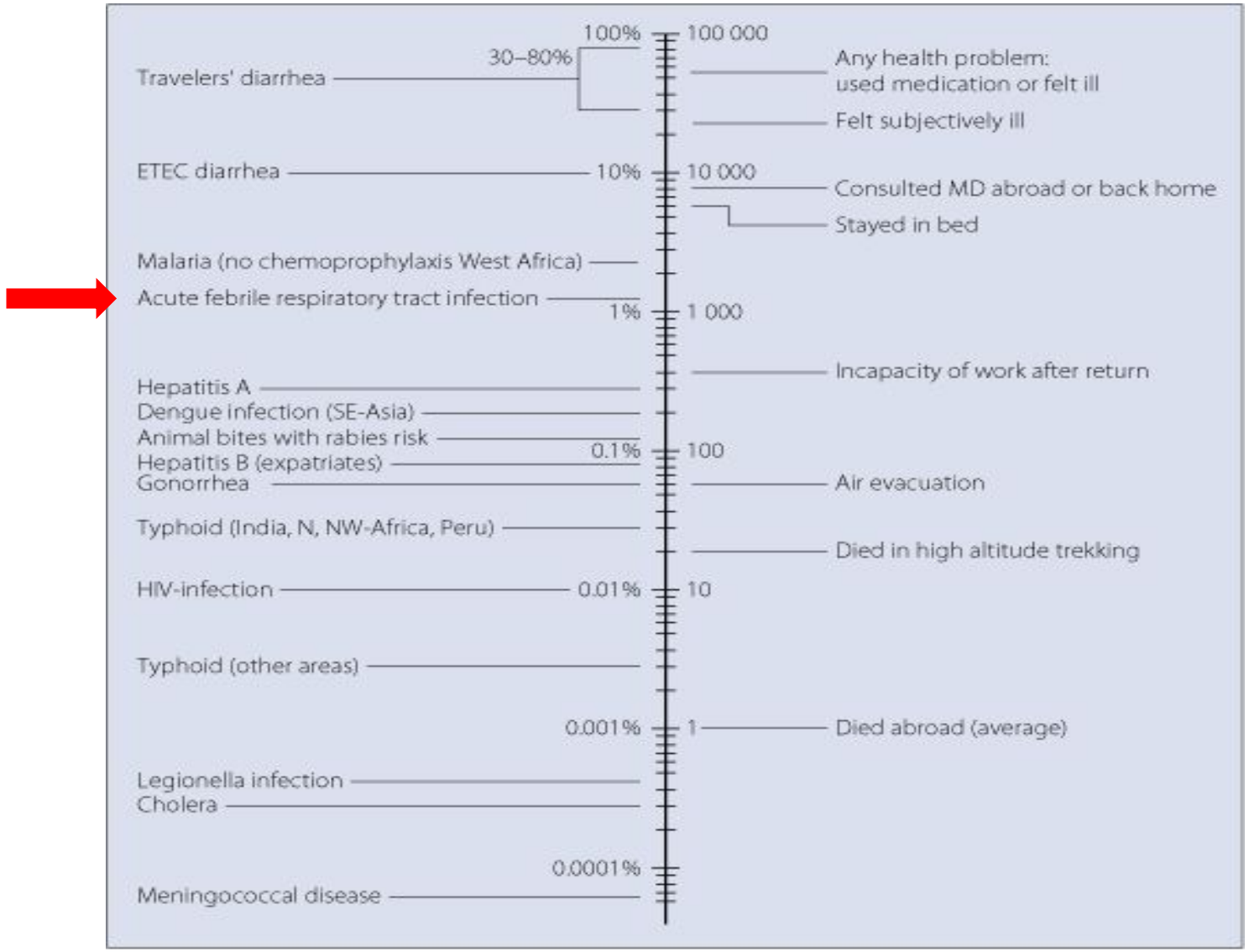
- Honoraria/advisor fees: Shoreland, Valneva, Sanofi, Merck
- Data Safety Monitoring Board: Valneva
- Royalties: "*Infectious Diseases: A Geographic Guide*"

Objective

- Provide overview of travel-related respiratory illness
- Describe travel-related influenza and Covid-19
- Discuss traveler-based genomic surveillance

Respiratory illnesses are reported commonly in travelers

Incidence rate per month of VPDs in travellers; best estimate for non-immunes



ORIGINAL RESEARCH | Annals of Internal Medicine

2013;158:456-468

GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011

Karin Leder, MBBS, MPH, PhD; Joseph Torresi, MBBS, PhD; Michael D. Libman, MD; Jakob P. Cramer, MD, MSc; Francesco Castelli, MD, PhD; Patricia Schlagenhauf, PhD; Annelies Wilder-Smith, MD, PhD, MIH; Mary E. Wilson, MD; Jay S. Keystone, MD, MSc; Eli Schwartz, MD; Elizabeth D. Barnett, MD; Frank von Sonnenburg, MD, PhD; John S. Brownstein, PhD; Allen C. Cheng, MBBS, PhD, MPH; Mark J. Sotir, PhD, MPH; Douglas H. Esposito, MD, MPH; and David O. Freedman, MD, for the GeoSentinel Surveillance Network*

Background: International travel continues to increase, particularly to Asia and Africa. Clinicians are increasingly likely to be consulted for advice before travel or by ill returned travelers.

Objective: To describe typical diseases in returned travelers according to region, travel reason, and patient demographic characteristics; describe the pattern of low-frequency travel-associated diseases; and refine key messages for care before and after travel.

Design: Descriptive, using GeoSentinel records.

Setting: 53 tropical or travel disease units in 24 countries.

Patients: 42 173 ill returned travelers seen between 2007 and 2011.

reason for travel, with travelers visiting friends and relatives in their country of origin having both a disproportionately high burden of serious febrile illness and very low rates of advice before travel (18.3%). Life-threatening diseases, such as *Plasmodium falciparum* malaria, melioidosis, and African trypanosomiasis, were reported.

Limitations: Sentinel surveillance data collected by specialist clinics do not reflect healthy returning travelers or those with mild or self-limited illness. Data cannot be used to infer quantitative risk for illness.

Conclusion: Many illnesses may have been preventable with appropriate advice, chemoprophylaxis, or vaccination. Clinicians can use these 5-year GeoSentinel data to help tailor more efficient pretravel preparation strategies and evaluate possible differential

2007-2011; n=42,173

Top exposure regions: Asia (33%), sub-Saharan Africa (27%)

Respiratory illness was #4 travel-related illness, reported in 11% of ill travelers (top 3: gastrointestinal diagnoses, febrile illness, and dermatologic disorder)

Study	Top illnesses (%)	% sought medical care	Hospitalization (%)
Chen et al (2016) n=400	Diarrhea (52), headache (26), fatigue (25), cough (24), runny/ stuffy nose (24)	18	<1
Wilkman et al (2016) n=363	TD, skin problem, fever, vomiting, respiratory infection	NA	1
Balaban et al (2014) n=33	Diarrhea (21), sore throat (11), nausea/vomiting (9), congestion/runny nose (8), coughing (7)	19	3
Dia et al (2010) n=313	Arthropod bite (62), diarrhea (46), sunburn (36), vomiting (9), cough (8)	11	<1
Rack et al (2006) n=282	GI (81), respiratory (32), fever (15), dermatologic (10)	16	<1
Hill (2010) n=501	Diarrhea (46), respiratory symptoms (26), skin (8), high altitude sickness (6), motion sickness (5)	8	3
Steffen et al (1987) n=1209	Severe diarrhea (56), vomiting/abd cramp (26), common cold (14), high fever several days (13), dermatosis (8)	55	1
Steffen et al (1985) n=7906	Diarrhea, constipation, respiratory infections, insomnia, headache	NA	NA

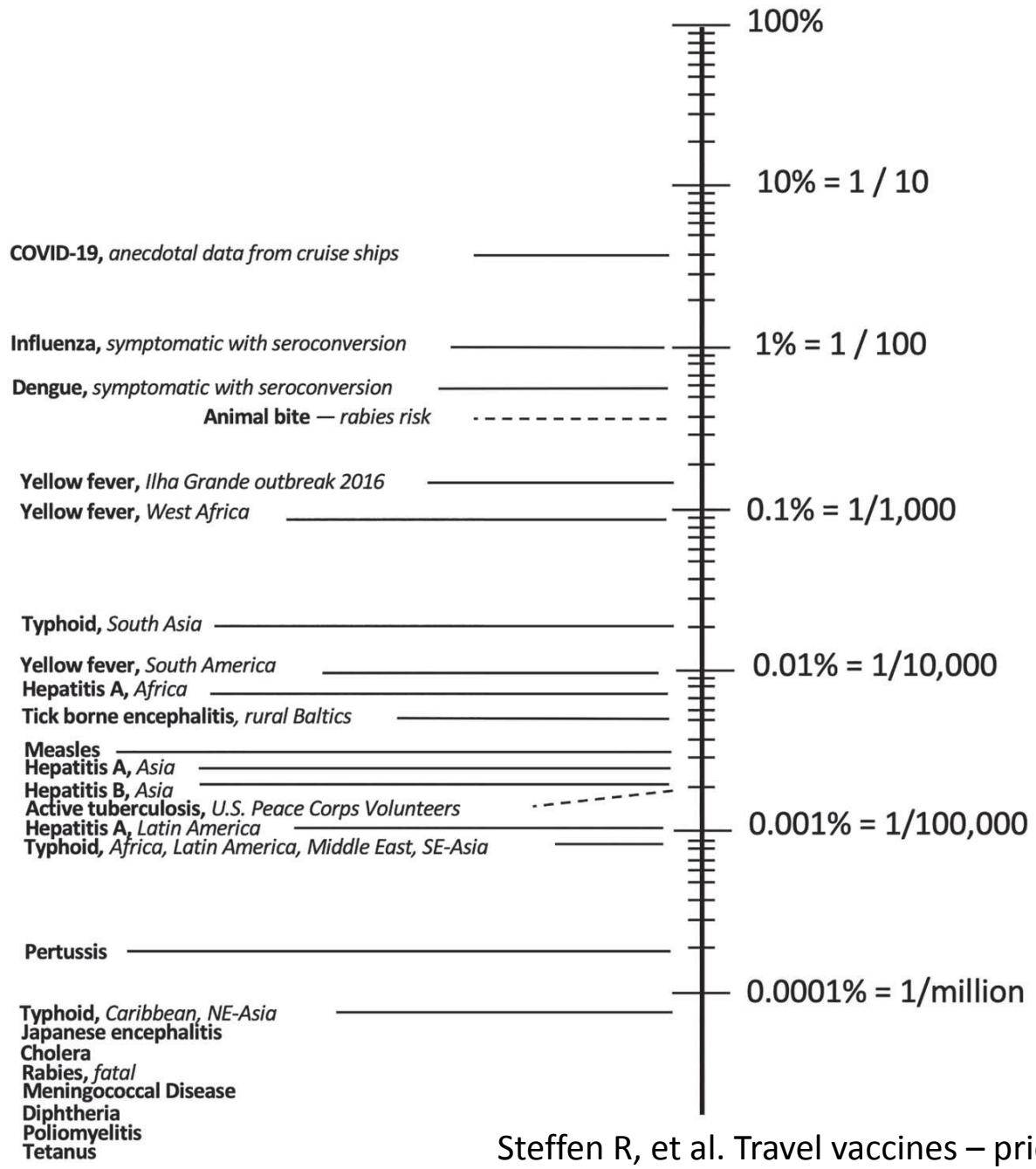
Angelo KM et al. JTM 2017;1-8.

Influenza in travelers

- Mutsch 2005: Seroconversion for influenza in 2.8% of all travelers; 1.2% had 4-fold rise in antibody titers. Incidence of 1.0 influenza-associated events/100 person-months abroad. 62.5% of seroconverters acquired influenza outside of European epidemic season.
- Belderok 2013: ILI attack rate = 0.8%. Incidence rate for ILI = 0.9%.
- Ratnam 2013: ARIs occurred in 28%; incidence = 106.4 ARIs/10,000 traveller days. 1% acquired influenza A during travel; incidence density = 3.4 infections/10,000 days of travel. 3.5-fold higher incidence of influenza in unvaccinated travellers compared to vaccinated travellers (p = 0.883).

Mutsch M et al. CID 2005; Belderock SM et al. EID 2013; Ratnam I et al. J Clin Virol 2013

Incidence rate per month of VPDs in travellers; best estimate for non-immunes



Steffen R, et al. Travel vaccines – priorities determined by incidence and impact. *J Travel Med 2023*

JTM Journal of Travel Medicine

Journal of Travel Medicine, 2023, 1–12
https://doi.org/10.1093/jtm/taad102
Review

Review

Influenza: seasonality and travel-related considerations

Loukas Kakoullis, MD, PhD, MPH[1,2], Robert Steffen, MD[3,4], Albert Osterhaus, DVM, PhD[5], Marco Goeijenbier, MD, PhD[6,7], Sowmya R. Rao, PhD[8], Satoshi Koiso, MDP, BVSc[9], Emily P. Hyle, MD, MSc[2,9,10], Edward T. Ryan, MD, DTM&H[2,10], Regina C. LaRocque, MD, MPH[2,10] and Lin H. Chen, MD[1,2,11]

Influenza seasonality varies globally

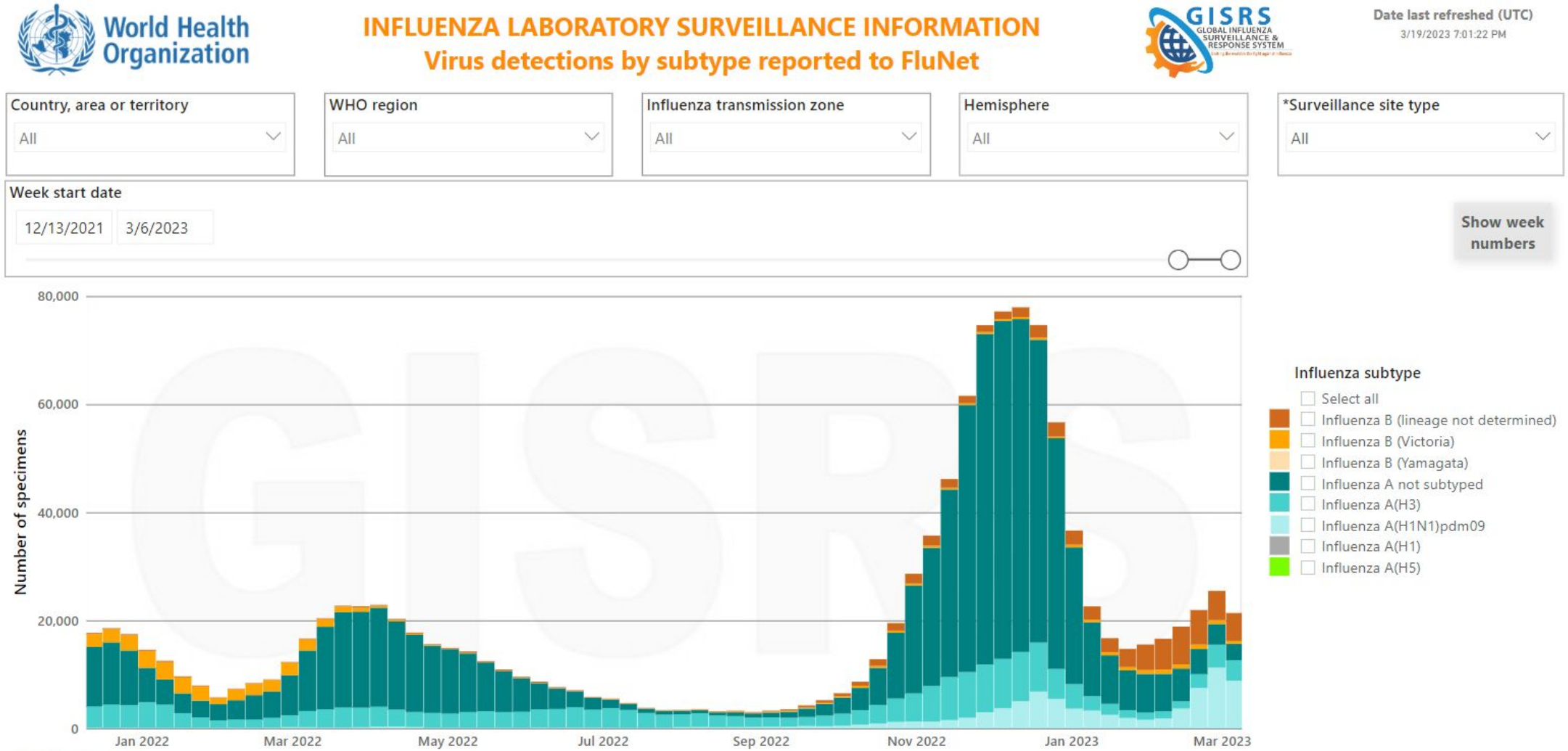
Temperate climate zones:

- Peaks October-April in Northern Hemisphere (NH)
- Peaks April-October in Southern Hemisphere (SH) More variable in tropics

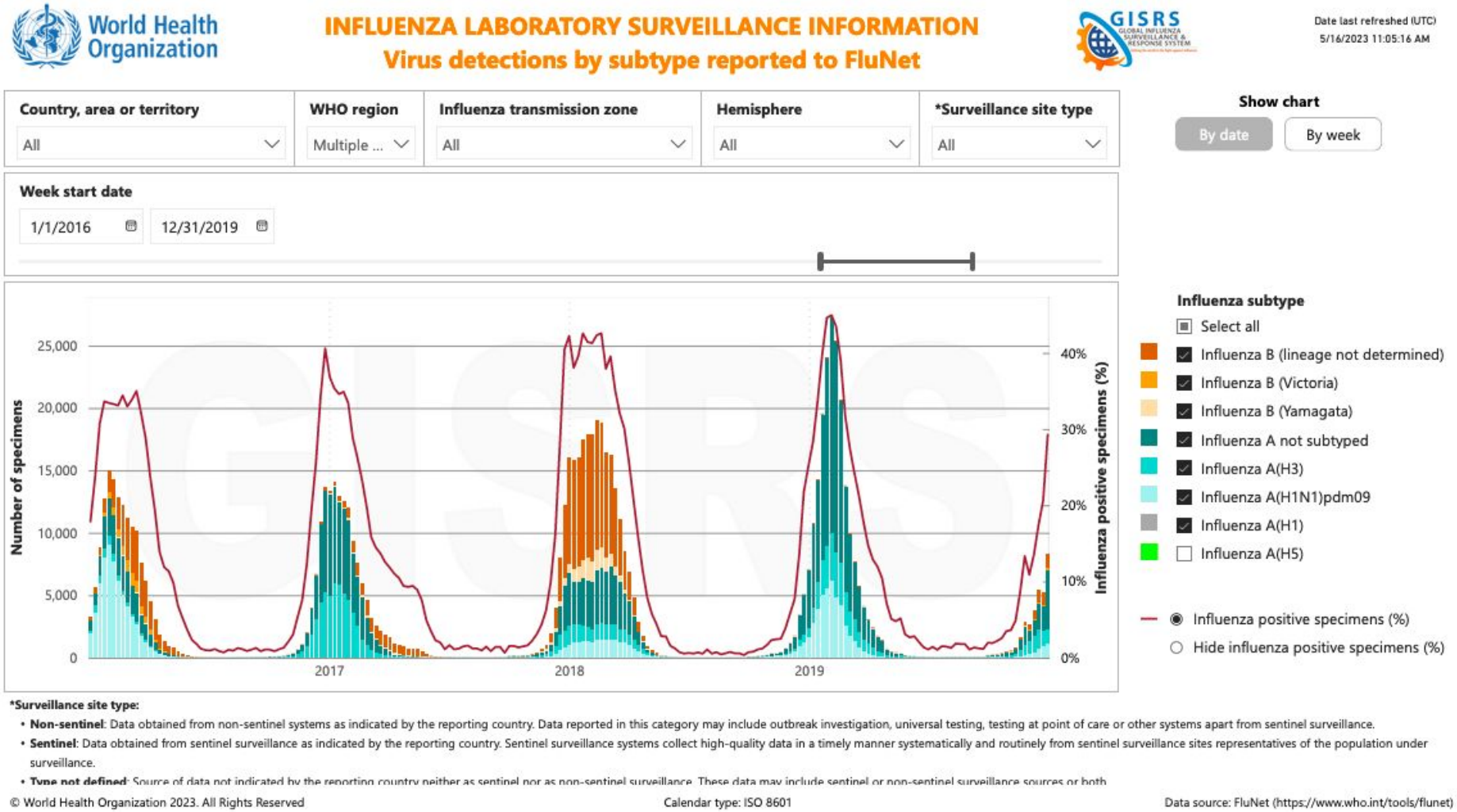
Occurs during travel, cruise and air travel-associated outbreaks

Travelers can have exposure with people from regions with ongoing influenza transmission

FluNet


World Health Organization
INFLUENZA LABORATORY SURVEILLANCE INFORMATION
Virus detections by subtype reported to FluNet
GISRS
GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM
Date last refreshed (UTC)
3/19/2023 7:01:22 PM
Country, area or territory
All
WHO region
All
Influenza transmission zone
All
Hemisphere
All
*Surveillance site type
All
Week start date
12/13/2021
3/6/2023
Show week numbers
Number of specimens
80,000
60,000
40,000
20,000
0
Jan 2022
Mar 2022
May 2022
Jul 2022
Sep 2022
Nov 2022
Jan 2023
Mar 2023
Influenza subtype
Select all
Influenza B (lineage not determined)
Influenza B (Victoria)
Influenza B (Yamagata)
Influenza A not subtyped
Influenza A(H3)
Influenza A(H1N1)pdm09
Influenza A(H1)
Influenza A(H5)
*Surveillance site type:
• Non-sentinel: Data obtained from non-sentinel systems as indicated by the reporting country. Data reported in this category may include outbreak investigation, universal testing, testing at point of care or other systems apart from sentinel surveillance.
• Sentinel: Data obtained from sentinel surveillance as indicated by the reporting country. Sentinel surveillance systems collect high-quality data in a timely manner systematically and routinely from sentinel surveillance sites representatives of the population under surveillance.
• Type not defined: Source of data not indicated by the reporting country neither as sentinel nor as non-sentinel surveillance. These data may include sentinel or non-sentinel surveillance sources or both.
© Copyright World Health Organization (WHO) [2022]. All Rights Reserved
Calendar type: ISO 8601
Data source: FluNet (https://www.who.int/tools/flunet)

EUR NH: November-May



***Surveillance site type:**

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Calendar type: ISO 8601

Data source: FluNet (https://www.who.int/tools/flunet)

AMR NH
October-May

AMR SH
March-October

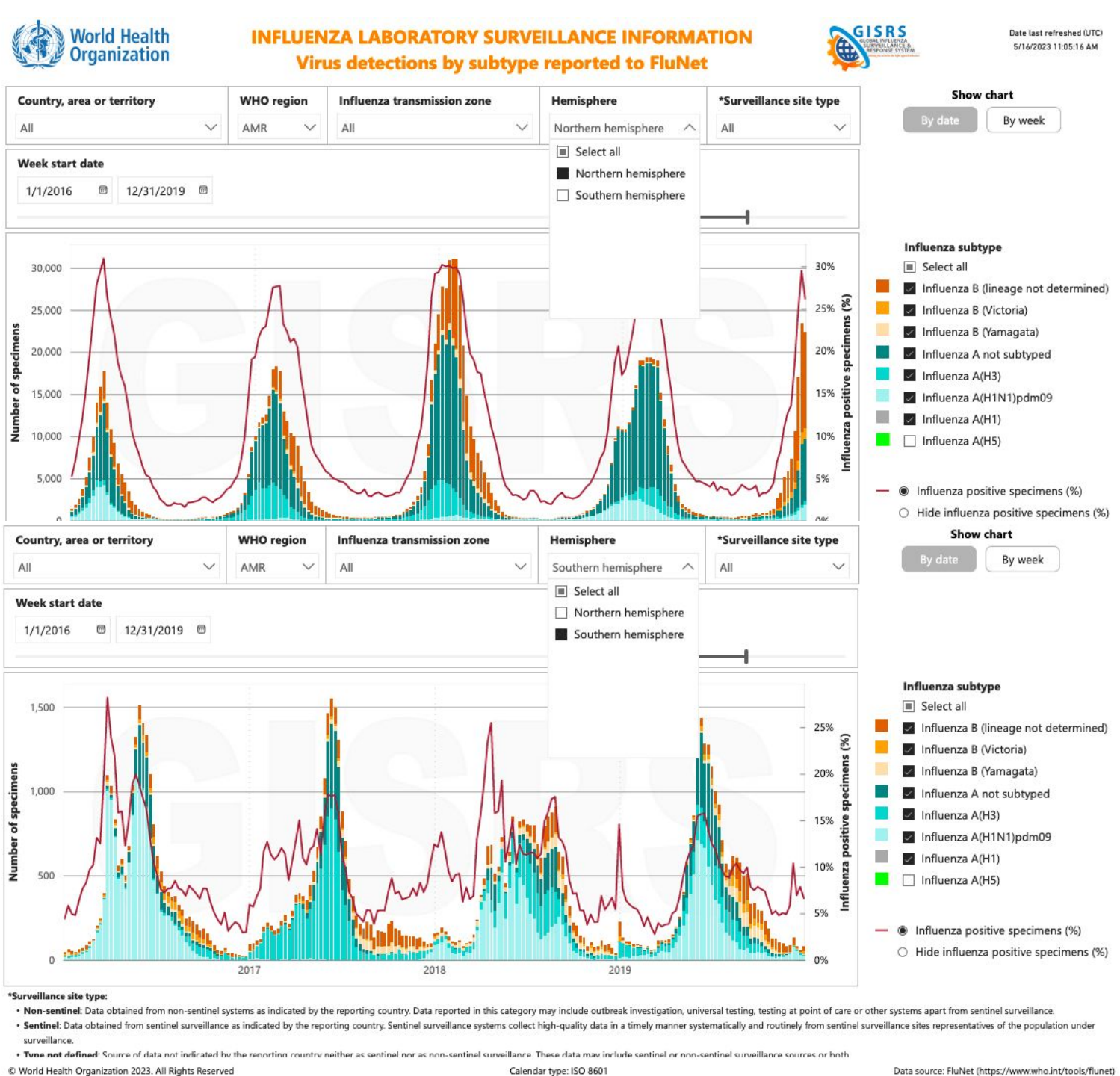


Table 2: FluNet data on peak influenza transmission periods for 2016-2019 in the 6 WHO regions, based on whether the country/territory is located in Northern or Southern Hemisphere.

WHO region	Northern Hemisphere	Southern Hemisphere
African Region (AFR)	September-April	April-September 2018: 2nd season Influenza B July-October
Region of the Americas (AMR)	October-May	March-October
South-East Asian Region (SEAR)	January-April, June-September (October in 2018)	January-June 2017: 2nd season September-December
European Region (EUR)	November-May	N/A
Eastern Mediterranean Region (EMR)	September-April	N/A
Western Pacific Region (WPR)	November-May/April 2017: 2nd season June-September	May-October

Air travel-related influenza

- May occur at start of trip, at airport, or through direct/indirect human contact
- 2009 H1N1 influenza pandemic: serologically-confirmed influenza occurred following flights, and in-flight transmission occurred among passengers sitting up to 2 rows from an index case
- Transmission could have occurred before or after flight while queuing for check-in, security screening, boarding/disembarking, or immigration, or in crowded bus to or from aircraft …
- High-efficiency particulate air (HEPA) ventilation systems should be effective in mitigating transmission risks when operated as recommended, though they may not be operating during boarding/disembarking

Goeijenbier M et al. J Travel Med 2017; Baker MG et al. BMJ 2010; Hertzberg VS et al. PNAS 2018; Young N et al. Influenza Other Resp Viruses 2014; ICAO. Aircraft Module 2021.

Cruise ship-related influenza

- >20 million cruise passengers/year
- 2nd most frequently reported infectious illness on cruise ships, after acute gastroenteritis
- Systematic review of 41 studies on respiratory virus transmission in transportation hubs and during transportation: influenza outbreaks on cruise ships affect 2-7% of passengers on board
- Rates of ARI or ILI vary between 0.2-37.1%.

Pavli A et al. TMAID 2016; Marshall CA et al. BMC Public Health 2016; Browne A et al. JTM 2016; Kakoullis L et al. JTM 2023

Examples of cruise ship-related influenza outbreaks

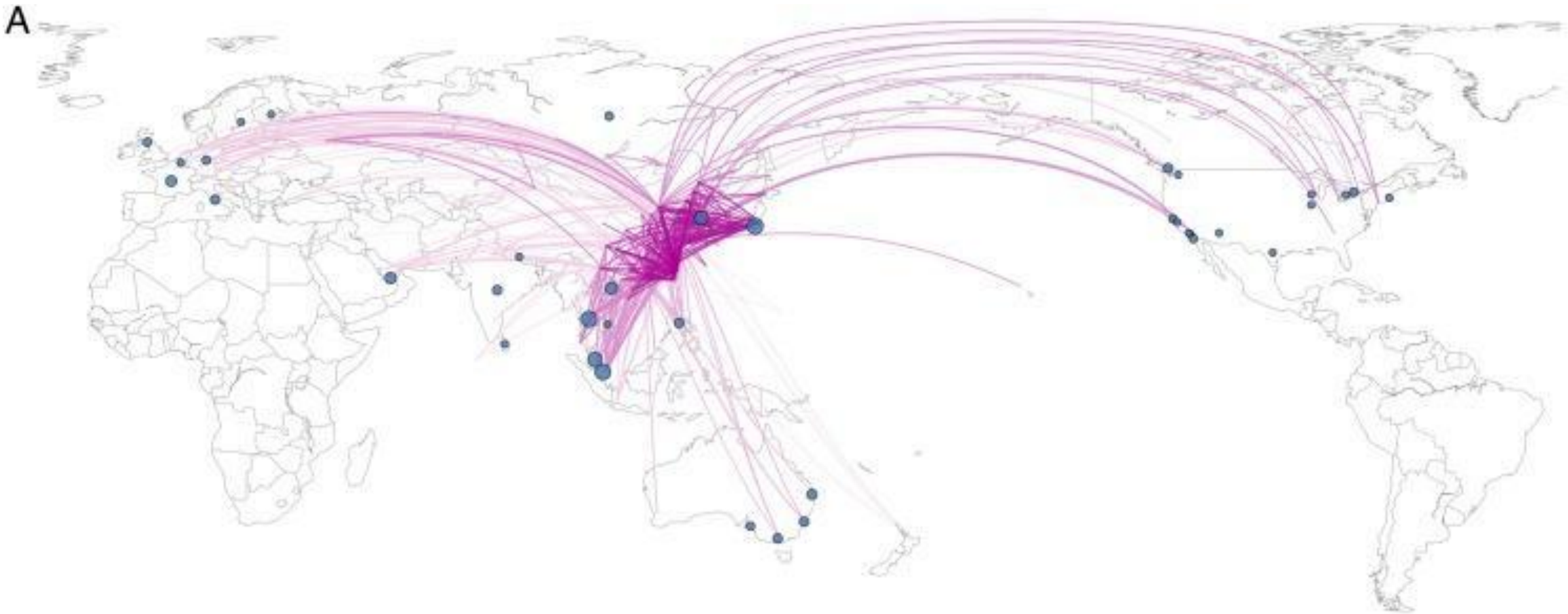
Period	Origin-destination	Study description	Virus strain	Number of cases (%)	Reference
Aug-Sep 1997	New York City-Montreal	Descriptions of outbreaks on 3 consecutive cruises of the same ship	A H3N2	ILI: Cruise 1: 39/1445 (2.7%) Cruise 2: 19/1448 (1.3%) Cruise 3: 3/1443 (0.2%)	Miller, 2000[48]
Jun-Jul 2000	UK-Russia-Germany	Description of outbreak on 1 ship	Not reported	ARI: 118/1817 (6.5%) ILI: 70/1817 (3.9%)	Christensen, 2001[49]
Sep 2000	Sydney-Noumea	Influenza testing and post-cruise survey of 1119 passengers (836 responders)	A and B	310/836 (37.1%) reported ILI. LCI: Influenza A: 40/1119 (3.6%) Influenza B: 7/1119 (0.6%)	Brotherton, 2003[47]
May 2009	Sydney-Pacific islands-Sydney	Descriptions of outbreaks on 2 consecutive cruises of the same ship	A H1N1 and H3N2	LCI: H1N1: 82/2704 (3%) H3N2: 98/2704 (3.6%)	Ward, 2010[50]
Feb 2012	Santos-coast of Brazil-Uruguay-Argentina	Description of outbreak on 1 ship	B	ARI: 104/2458 (4.2%) LCI: 6/2458 (0.2%)	Fernandes, 2014[46]
Mar-Apr 2014	South America -Los Angeles	Description of outbreaks on 2 ships	A H3N2, A H1N1, B	Ship A: ARI: 130/3652 (3.6%) LCI: 35/3652 (0.9%) Ship B: ARI: 241/4144 (5.8%) LCI:11/4144 (0.3%)	Millman, 2015[51]
May-Sep 2013-2015	Alaska	Surveillance of infirmaries of 6 cruise ships	A H1N1, A H3, B	LCI: 292/410 (71.2%) of ARI. Influenza A (H1N1): 30/410 (7.3%) Influenza A H3: 212/410 (51.7%) Influenza B: 56/410 (13.7%)	Rogers, 2017[45]
2020	Kobe to Yokohama, Japan (circum- navigation, 23 ports in 20 countries)	Description of outbreak on 1 ship	A	LCI: 34/1275 (2.7%)	Aoki, 2021[52]

Adapted from Kakoullis L et al. JTM 2023

Covid-19 and travel: Diamond Princess experience

- 3711 passengers & crew tested:
  - 1/5+ (nearly half no symptoms at test)
  - 18% of + never developed symptoms
- 381 had symptoms/test+:
  - 10% needed intensive care
  - 1.3% died (all >70 years old)

Covid-19 early epidemiology: international spread



The blue circles indicate the number of international confirmed cases. Size of circles is proportional to the number of confirmed SARS-CoV-2 cases with travel history to China as of February, 15, 2020.

Wells CR et al. PNAS 2020

Covid-19 via air travel and quarantine-isolation facilities

Air travel and quarantine-isolation facilities			
March 2020	UK	Vietnam	1 index case, followed by 16 cases among 201 passengers and 16 crew
March 2020	USA	Hong Kong	4 cases (2 passengers among 294 passengers, and 2 crew)
March 2020	Australia	Australia	29 cases PCR-confirmed (among 241 passengers on board)
September 2020	India	New Zealand	Index cases tested positive in MIQ @3 days after flight, followed by sequential identification of 7 additional cases in MIQ and in the community
September-October 2020	UAE	New Zealand	7 positive PCRs among 86 passengers on a flight from Dubai, UAE
December 2020	International	Ireland	165 cases on 134 flights; 40% symptomatic on board
April 2021	India	Hong Kong	59 PCR-confirmed cases among 146 passengers; 20% symptomatic
April 2021	India	Australia	47 cases aboard 2 flights carrying 345 passengers; 14% of arrival cases symptomatic
April-June 2021	International	Spain	196 PCR-confirmed among 45,211 travelers initially tested by rapid antigen on arrival to Madrid international airport
July 2021	Philippines, United Arab Emirates	New Zealand	Traveler A arrived from the Philippines and traveler E from a 5-person travel group (BCDEF) from UAE tested positive. Travelers B, C, D subsequently tested positive; viral sequences matched A.

Adapted from Flaherty GT et al. Curr Infect Dis Rep 2022

Covid-19 via cruise ship-related

Arrival date / incident date	Origin	Incident location	Number of cases	Comments
January-February 2020	Japan	Hong Kong, Japan	Diamond Princess: 712 cases (554 of 2666 guests, 152 of 1045 crew), 9 deaths	Of 437 Americans and their travel companions on ship, 114 (26%) were SARS-CoV-2-positive. Attack rate=18% in those without infected cabinmates vs. 63% with asymptomatic infected cabinmate vs 81% with symptomatic infected cabinmate. Estimated infection rate was 79% if no intervention had been implemented.
February-March 2020	USA	USA	Grand Princess 2 voyages: 123 cases (among 2422 guests and 1111 crew) and 5 deaths	Only 30% of guests and crew were tested. Of 469 persons with available test results, 78 (16.6%) were SARS-CoV-2-positive.
March 2020	Australia	Australia	Ruby Princess: 907 primary cases (605 of 2647 guests and 202 Of 1151 crew), 29 deaths	120 people on board the Ruby Princess met the case definition for COVID-19 at the time of disembarkment; in April 2020, the outbreak was linked to 13% of all COVID-19 cases in Australia.
July-August 2020	Norway	Norway	MS Roald Amundsen: 42 cases among 167 crewmembers and 28 cases among 391 passengers (attack rates 25.2% and 7.2%, respectively)	Outbreaks of lineage B.1.36 occurred on 2 1-week voyages, from Tromsø around the Svalbard archipelago.

Adapted from Flaherty GT et al. Curr Infect Dis Rep 2022

CDC Epidemic Intelligence Service (EIS) Conference April 24–27, 2023: 1,800 in-person & 400 virtual attendees

- May 5–12 survey of COVID-19 test results and healthcare-seeking behavior: 1,443 respondents (>80% of in-person attendees)
- 181 (13%) reported testing positive for SARS-CoV-2
  - 52% reported no known prior COVID-19 infection
  - 27% of those who tested positive received antiviral medications
- 1,435 (99.4%) reported at least one COVID-19 vaccine dose
- 70% reported not wearing a mask
- None were hospitalized

https://www.cdc.gov/media/releases/2023/s0526-eis.html

Covid-19 and travelers: evolving situation

- No published systematically studied incidence rates on travelers relative to:
  - Vaccination – last dose
  - Variant-specific rate
  - Unvaccinated/infection-naïve

- Rates likely will continue to change

TGS: Traveler-based Genomic Surveillance

1. Arriving international travelers volunteer to self-collect nasal swab.
2. Samples shipped to lab for SARS-CoV-2 RT-PCR.
3. Positive samples undergo whole genome sequencing to determine variants.
4. Select TGS samples are shared with CDC lab, undergo viral characterization (re new variant's transmissibility, virulence, response to current treatments or vaccines).

https://wwwnc.cdc.gov/travel/page/travel-genomic-surveillance

Airplane wastewater sampling for TGS

- Wastewater surveillance: effective, low-cost
- No direct involvement/participation from travelers to obtain samples
- Since August 2022, CDC has conducted airplane wastewater sampling.

Process

1. Wastewater is collected using custom-made collection device.
2. Samples are shipped to laboratory for RT-PCR.
3. Positive samples undergo whole genome sequencing to determine variants.

Airport triturator drain sampling

- Wastewater samples collected at airport using automated sampler device at the airport triturator.
- The triturator is a consolidation point, which captures wastewater samples from multiple flights and does not include airport terminal waste.
- Started April 2023 at SFO

US map of airports in TGS:

- Nasal swab only: Los Angeles, Newark, Seattle, Washington, DC (IAD)
- Triturator only: Boston
- Nasal swab + triturator: San Francisco
- Nasal swab + wastewater: NYC (JFK)

TGS: Traveler-based Genomic Surveillance

- **Provides early warning system**
  TGS detected Omicron variants up to 6 weeks before they were reported globally.
- **Quickly provides information to public health authorities and samples to US federal labs**
  TGS is #2 contributor in US to SARS-CoV-2 genomic sequences.
- **Fills gaps in global surveillance when testing and sequencing data are not available**
  TGS enrolls ~300,000 travelers/year from >135 countries from all WHO regions.
- **Prevents spread of communicable diseases**
  December 2022 surge of COVID-19 in China: TGS expanded rapidly to additional airports to cover >250 flights from China and surrounding transportation hubs to quickly gather samples and provide information on circulating variants in China.

Finally, travel as a loop

- Consider encountering other travelers originating from regions with ongoing transmission

- Exposure at destination and en route

Summary

- Influenza and Covid-19 are top vaccine-preventable infections associated with international travel
- Systematic studies are still needed on incidence rates
- Traveler-based surveillance can provide valuable information on outbreaks
- Encourage prevention strategies including vaccination

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