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
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

- Travelers’ diarrhea: 30–80% (100,000)
- ETEC diarrhea: 10% (10,000)
- Malaria (no chemoprophyaxis West Africa): 1% (1,000)
- Acute febrile respiratory tract infection
- Hepatitis A
- Dengue infection (SE Asia)
- Animal bites with rabies risk
- Hepatitis B (expatriates)
- Gonorrhea
- Typhoid (India, N, NW-Africa, Peru)
- HIV-infection: 0.01% (10)
- Typhoid (other areas)
- Legionella infection
- Cholera
- Meningococcal disease: 0.0001% (1)

Any health problem: used medication or felt ill
Felt subjectively ill
Consulted MD abroad or back home
Stayed in bed
Incapacity of work after return
Air evacuation
Died in high altitude trekking
Died abroad (average)
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)
<table>
<thead>
<tr>
<th>Study</th>
<th>Top illnesses (%)</th>
<th>% sought medical care</th>
<th>Hospitalization (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al (2016) n=400</td>
<td>Diarrhea (52), headache (26), fatigue (25), cough (24), runny/ stuffy nose (24)</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Wilkman et al (2016) n=363</td>
<td>TD, skin problem, fever, vomiting, respiratory infection</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Balaban et al (2014) n=33</td>
<td>Diarrhea (21), sore throat (11), nausea/vomiting (9), congestion/runny nose (8), coughing (7)</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Dia et al (2010) n=313</td>
<td>Arthropod bite (62), diarrhea (46), sunburn (36), vomiting (9), cough (8)</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rack et al (2006) n=282</td>
<td>GI (81), respiratory (32), fever (15), dermatologic (10)</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hill (2010) n=501</td>
<td>Diarrhea (46), respiratory symptoms (26), skin (8), high altitude sickness (6), motion sickness (5)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Steffen et al (1987) n=1209</td>
<td>Severe diarrhea (56), vomiting/abd cramp (26), common cold (14), high fever several days (13), dermatosis (8)</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>Steffen et al (1985) n=7906</td>
<td>Diarrhea, constipation, respiratory infections, insomnia, headache</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
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 ($p = 0.883$).
Incidence rate per month of VPDs in travellers; best estimate for non-immunes

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
EUR NH: November-May
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.

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

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

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Origin Country</th>
<th>Destination Country</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2020</td>
<td>UK</td>
<td>Vietnam</td>
<td>1 index case, followed by 16 cases among 201 passengers and 16 crew</td>
</tr>
<tr>
<td>March 2020</td>
<td>USA</td>
<td>Hong Kong</td>
<td>4 cases (2 passengers among 294 passengers, and 2 crew)</td>
</tr>
<tr>
<td>March 2020</td>
<td>Australia</td>
<td>Australia</td>
<td>29 cases PCR-confirmed (among 241 passengers on board)</td>
</tr>
<tr>
<td>September 2020</td>
<td>India</td>
<td>New Zealand</td>
<td>Index cases tested positive in MIQ @3 days after flight, followed by sequential identification of 7 additional cases in MIQ and in the community</td>
</tr>
<tr>
<td>September-October 2020</td>
<td>UAE</td>
<td>New Zealand</td>
<td>7 positive PCRs among 86 passengers on a flight from Dubai, UAE</td>
</tr>
<tr>
<td>December 2020</td>
<td>International</td>
<td>Ireland</td>
<td>165 cases on 134 flights; 40% symptomatic on board</td>
</tr>
<tr>
<td>April 2021</td>
<td>India</td>
<td>Hong Kong</td>
<td>59 PCR-confirmed cases among 146 passengers; 20% symptomatic</td>
</tr>
<tr>
<td>April 2021</td>
<td>India</td>
<td>Australia</td>
<td>47 cases aboard 2 flights carrying 345 passengers; 14% of arrival cases symptomatic</td>
</tr>
<tr>
<td>April-June 2021</td>
<td>International</td>
<td>Spain</td>
<td>196 PCR-confirmed among 45,211 travelers initially tested by rapid antigen on arrival to Madrid international airport</td>
</tr>
<tr>
<td>July 2021</td>
<td>Philippines, United Arab Emirates</td>
<td>New Zealand</td>
<td>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.</td>
</tr>
</tbody>
</table>

Adapted from Flaherty GT et al. Curr Infect Dis Rep 2022
## Covid-19 via cruise ship-related

<table>
<thead>
<tr>
<th>Arrival date / incident date</th>
<th>Origin</th>
<th>Incident location</th>
<th>Number of cases</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>January-February 2020</td>
<td>Japan</td>
<td>Hong Kong, Japan</td>
<td>Diamond Princess: 712 cases (554 of 2666 guests, 152 of 1045 crew), 9 deaths</td>
<td>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.</td>
</tr>
<tr>
<td>February-March 2020</td>
<td>USA</td>
<td>USA</td>
<td>Grand Princess 2 voyages: 123 cases (among 2422 guests and 1111 crew) and 5 deaths</td>
<td>Only 30% of guests and crew were tested. Of 469 persons with available test results, 78 (16.6%) were SARS-CoV-2-positive.</td>
</tr>
<tr>
<td>March 2020</td>
<td>Australia</td>
<td>Australia</td>
<td>Ruby Princess: 907 primary cases (605 of 2647 guests and 202 of 1151 crew), 29 deaths</td>
<td>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.</td>
</tr>
<tr>
<td>July-August 2020</td>
<td>Norway</td>
<td>Norway</td>
<td>MS Roald Amundsen: 42 cases among 167 crewmembers and 28 cases among 391 passengers (attack rates 25.2% and 7.2%, respectively)</td>
<td>Outbreaks of lineage B.1.36 occurred on 2 1-week voyages, from Tromsø around the Svalbard archipelago.</td>
</tr>
</tbody>
</table>

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

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
Learning @ ISTM is the destination for all ISTM educational offerings.

- ISTM Webinars
- CISTM Videos
- ISTM Resource Library

- Travel Medicine Review & Update Course
- Travel Medicine Podcast