

only non-nephrotic proteinuria (urinary protein excretion, 1 g per day) persisted, with a serum creatinine level of 108 μ mol per liter. Positron-emission tomography showed that the subcutaneous metastases had disappeared and the right inguinal lymph node had stabilized.

The timing of the illness suggested that CTLA4 antibodies had a role. The patient had had no evidence of proteinuria during a period of several years when the melanoma was developing, yet glomerulonephritis occurred shortly after treatment with ipilimumab was started. Circulating anti-double-stranded DNA antibodies appeared concomitantly and regressed after ipilimumab was withdrawn.

CTLA4 is a coreceptor expressed by activated, memory, and regulatory T cells, and it has a key role in down-regulating T-cell activation.¹ Anti-CTLA4 antibodies are promising antitumor-response stimulators. Several side effects have been reported in patients receiving anti-CTLA4 antibodies, including enterocolitis, thyroiditis, and hypophysitis,² which have been related to severe inflammatory-cell infiltrates. However, it was not a cellular infiltrate but rather an immune-com-

plex-mediated kidney injury that was detected in our patient. Both circulating anti-double-stranded DNA antibodies and glomerular IgG and C3 deposits have been reported in mice treated with anti-CTLA4 antibodies.³ Because of the increasing use of anti-CTLA4 antibodies, clinicians should be aware of this potentially severe complication.

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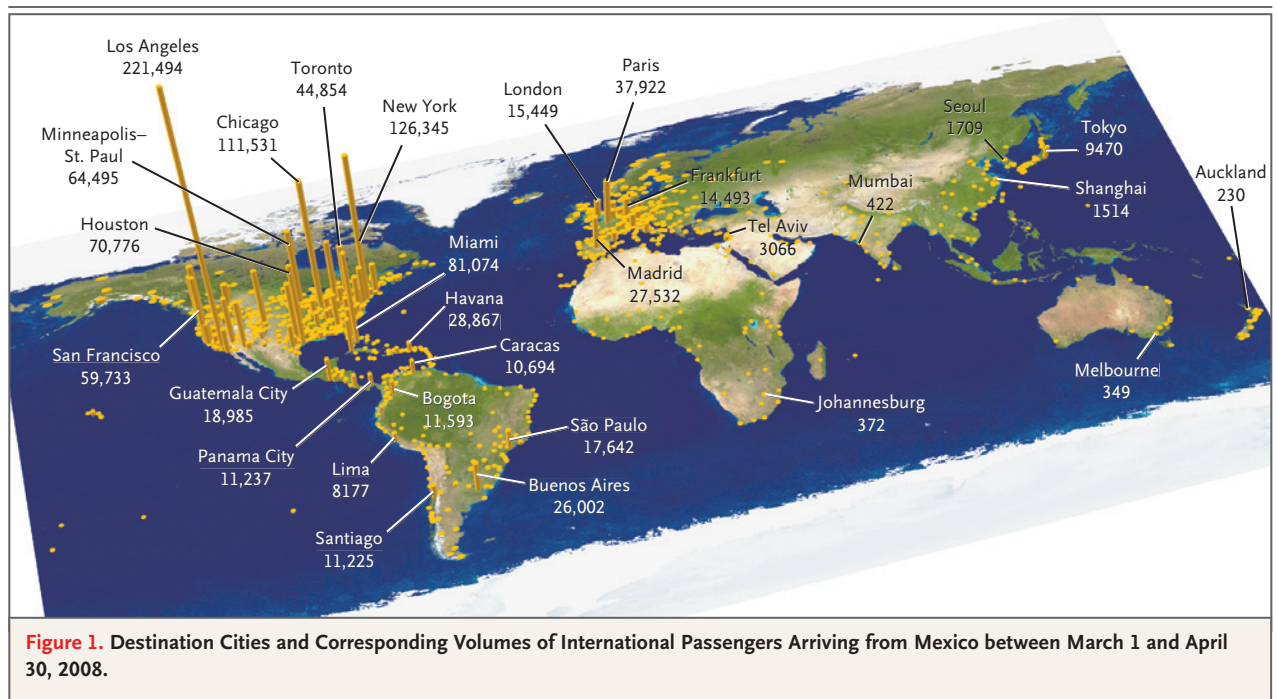
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Spread of a Novel Influenza A (H1N1) Virus via Global Airline Transportation

TO THE EDITOR: Throughout March and April 2009, international air travelers departing from Mexico were unknowingly transporting a novel influenza A (H1N1) virus¹ to cities around the world. We analyzed the flight itineraries for all passengers departing from commercial airports in Mexico between March and April 2008, using data from the International Air Transport Association (IATA). The purpose of this analysis was to show how travelers — and consequently to predict how H1N1 — would disseminate worldwide during the initial wavefront of this epidemic. We analyzed IATA data from March and April 2008 for the following reasons: the data accounted for more than 95% of all passenger trips worldwide

via commercial airlines, they included information on the flight origins and destinations of actual passengers, data on passenger itineraries for the period from March through April 2009 were unavailable at the time of this analysis, the global pattern of passenger departures from Mexico between March and April varies minimally from year to year, and the epidemic in Mexico was largely unrecognized during the period from March through April 2009, with passenger departures presumably following their usual seasonal pattern.

Our analysis showed that in March and April 2008, a total of 2.35 million passengers flew from Mexico to 1018 cities in 164 countries (Fig. 1, and Table 1 in the Supplementary Appendix, avail-



able with the full text of this letter at NEJM.org). A total of 80.7% of passengers had flight destinations in the United States or Canada; 8.8% in Central America, South America, or the Caribbean Islands; 8.7% in Western Europe; 1.0% in East Asia; and 0.8% elsewhere. These flight patterns were very similar to those during the same months in 2007 (see Fig. 1 in the Supplementary Appendix). We then compared the international destinations of travelers departing from Mexico with confirmed H1N1 importations associated with travel to Mexico, and we found a remarkably strong degree of correlation. Of the 20 countries worldwide with the highest volumes of international passengers arriving from Mexico, 16 had confirmed importations associated with travel to Mexico as of May 25, 2009 (Table 1). A receiver-operating-characteristic (ROC) curve plotting the relationship between international air-traffic flows and H1N1 importation revealed that countries receiving more than 1400 passengers from Mexico were at a significantly elevated risk for impor-

tation. With the use of this passenger threshold, international air-traffic volume alone was more than 92% sensitive and more than 92% specific in predicting importation, with an area under the ROC curve of 0.97 (see Fig. 2 in the Supplementary Appendix).

Although the correlation between the international movements of travelers and H1N1 is generally intuitive, our findings suggest that quantitative analysis of worldwide air-traffic patterns can help cities and countries around the world better anticipate their risks of importing global infectious diseases. In response to the outbreak of the severe acute respiratory syndrome in Toronto, an initiative called the Bio.Diaspora Project² was developed to conduct rapid assessments of global infectious-disease alerts³ or confirmed epidemics by evaluating the probable pathways of international dissemination from any commercial airport worldwide at any point in time. Operating under the framework of the revised International Health Regulations,⁴ the initiative also

Table 1. Countries Receiving the Largest Numbers of Passengers from Mexico during March and April 2008 and Importation of the Influenza A (H1N1) Virus Associated with Travel to Mexico (as of May 25, 2009).

Country Rank	Country	No. of Passengers Arriving from Mexico	Confirmed Importation of Influenza A (H1N1) Virus
1	United States	1,744,665	Yes
2	Canada	149,137	Yes
3	France	47,501	Yes
4	Spain	42,815	Yes
5	Germany	33,448	Yes
6	Cuba	29,123	Yes
7	Argentina	28,789	Yes
8	Italy	24,252	Yes
9	Brazil	23,125	Yes
10	Guatemala	19,719	Yes
11	United Kingdom	17,993	Yes
12	Colombia	16,583	Yes
13	Japan	12,014	No*
14	Chile	11,499	No*
15	Venezuela	11,464	No†
16	Panama	11,238	Yes
17	Costa Rica	10,912	Yes
18	Netherlands	8,942	Yes
19	Peru	8,356	No*
20	Switzerland	6,576	Yes

* As of May 25, 2009, Japan, Chile, and Peru reported 343, 74, and 25 confirmed cases of H1N1 influenza virus infection, respectively, although no known associations with travel to Mexico were identified.

† As of May 25, 2009, Venezuela had no reported cases of confirmed H1N1 influenza virus infection.

examines how countries are connected by shared risks of importing global infectious diseases and considers the implications for potential shared responsibilities that could strengthen the fabric of public health security in the world.⁵

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