

confidential information such as private patient attributes, commercial company details, and metadata surrounding precise collection points. Such an arrangement could easily conform to a real-time, data-sharing model for Europe as well.

One of our main concerns is that, although Pijnacker and colleagues<sup>2</sup> reported in the appendix to their study that FASTQ reads from all sequences in their study were deposited in NCBI (BioProject PRJNA248792), these data were not released during the outbreak investigation to allow direct comparisons to other publicly available data. We have observed closely related WGS clusters (ten or fewer SNPs) linked to illnesses, including isolates from contaminated food or the environment, from 72 countries including Australia,<sup>7</sup> Austria, Brazil, Canada,<sup>8</sup> Chile, China, Dominican Republic, Ecuador, Egypt, Ethiopia, India, Indonesia, Italy, Kenya, Mexico, Peru, the Philippines, Switzerland, Thailand, Turkey, Uganda, Vietnam, and the UK, but not Poland. When the release of data is delayed, determining epidemiological linkages becomes more difficult. We also disagree that technical barriers preclude the uploading of WGS data. It is our opinion that the benefit of publicly sharing WGS data in real time is vital for global public health. However, we do agree with the need to harmonise data interpretation and analyses, as is evident between the numerous US agencies that are engaged in GenomeTrakr and NCBI Pathogen Detection.<sup>9,10</sup> Indeed, there is an acute need to increase international harmonisation of WGS methods for maximising the benefit of global data sharing and use.<sup>11,12</sup>

Finally, Pijnacker and colleagues<sup>2</sup> note that it is likely that 12 non-EU countries were affected by the outbreak but were not detected because molecular typing is not routinely done in many countries. We would add that many countries with the infrastructure

for WGS do not share their data globally in real time. The regional privatisation and emphasis on internal WGS databases, although useful locally, will only hinder more widespread epidemiological investigations to the detriment of global food safety and public health.<sup>13</sup>

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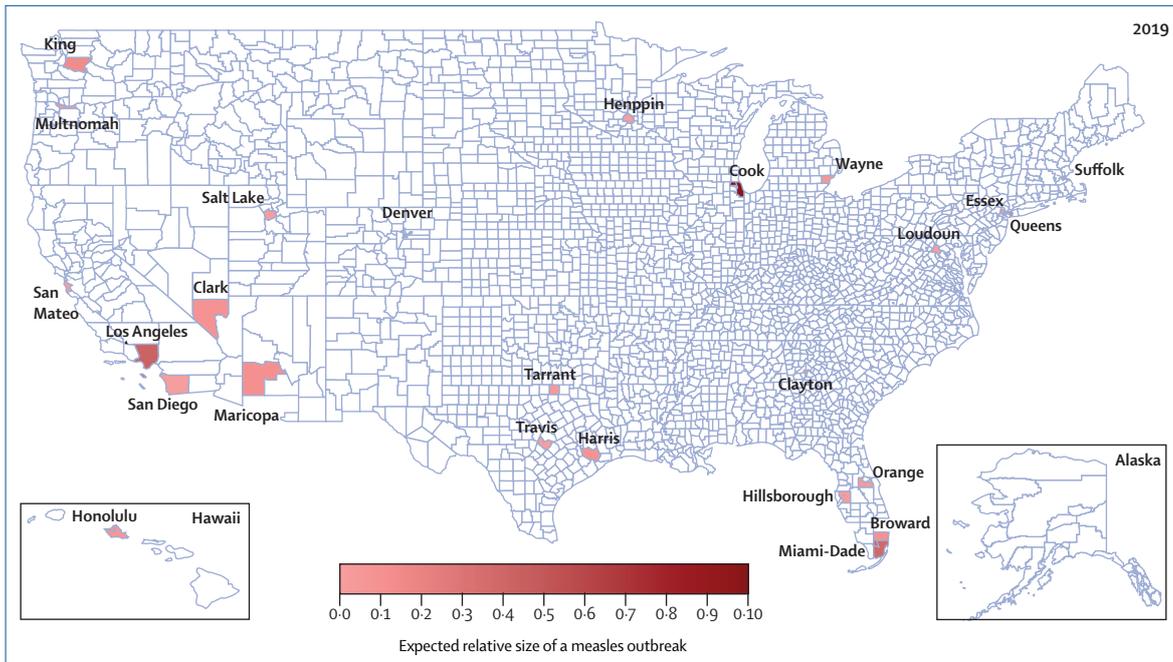


## Measles resurgence in the USA: how international travel compounds vaccine resistance

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Hotez and colleagues<sup>1</sup> recent article highlights the increasing frequency of vaccine-preventable disease cases in Europe and the USA caused by very visible anti-vaccine movements.<sup>2</sup> The most troubling aspect of this

development is the global increase in measles cases. From Jan 1, 2019, to April 26, 2019, the USA reported 704 confirmed measles cases spanning 22 states, compared with 372 reported cases in 2018, 120 in 2017,



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**Figure:** Top 25 US counties predicted to be at the highest risk of measles in 2019

Results from the analysis use air travel data from 2017, which was the most recently available for this analysis, and international measles outbreak data from 2019. Risk is measured by the expected relative size of a measles outbreak.

86 in 2016, 188 in 2015, and 667 in 2014.<sup>3</sup> Therefore, only 4 months into 2019 the number of cases reported is already the highest since measles was declared officially eliminated in the US in 2000.<sup>3</sup>

These high numbers show that the USA still remains at risk for large measles epidemics such as those recently seen in Europe.<sup>1</sup> Two main factors are believed to contribute to the resurgence of measles cases in the USA: reintroduction of the virus at individual localities through travel from countries experiencing outbreaks<sup>4</sup> and low vaccination rates fueled by non-medical exemptions (NMEs).<sup>1</sup> The analysis we present confirms the hypothesis that these two factors are the most salient ones for the outbreaks of measles in the USA in 2019. This hypothesis allows a predictive risk analysis to identify which US regions are most at risk. The seriousness of this risk is underscored by the ease of transmission of measles, which is caused by the highly contagious measles morbillivirus that is capable of airborne spread.<sup>5</sup>

We explain this risk using a quantitative model that identifies the US counties with the highest risk of a measles outbreak in 2019. This spatial relative risk profile at a county resolution for the USA is derived from a multiplicative risk function that compounds four factors:

international air travel volume to the destination county,<sup>6</sup> NME rates in the county,<sup>2,7</sup> county population,<sup>8</sup> and the incidence rate of the measles outbreak at travel origin.<sup>9,10</sup> The model uses county level NME rates if available;<sup>2</sup> otherwise, it relies on state averages for NME rates or estimated vaccination rates.<sup>7</sup> A detailed description of the data and methods used are available in the appendix. Our risk measure can be interpreted as the expected relative size of a measles outbreak in a county.

The results of the predictions are shown in the figure and listed in the appendix. The results of our calculation are spatially consistent with the reported measles cases in the USA (last comparison made April 15, 2019): counties we identify or those immediately adjacent to them have reported measles cases in 2019. According to the Centers for Disease Control and Prevention and various state health departments,<sup>3</sup> at least 45 USA counties have reported measles cases in 2019 and 30 of these are either included in the top 25 at-risk counties identified in figure 1 or spatially adjacent to one of the top 25 counties. Our results correctly predicted the areas in Washington, Oregon, and New York that have had major measles outbreaks. Brooklyn, New York, which has reported over 300 cases,<sup>3</sup> is adjacent to Queens, New York, which ranked fourth. Multnomah, Oregon

See Online for appendix

is ranked 13th, and adjacent to Clark, Washington with 73 cases.<sup>3</sup> San Mateo, California, ranked 19th has had an outbreak with four cases; adjacent Santa Clara has also reported four cases, and adjacent Santa Cruz and San Francisco have also each reported one case. Several Texas counties are identified as being at an elevated risk of measles. Harris, Texas has had the biggest outbreak so far with four cases<sup>3</sup> and is ranked ninth in our predictions. Another seven counties in Texas have reported cases, which are all in close proximity to either Tarrant, Texas (ranked 12th) or Travis, Texas (ranked 22nd).

Further, each of the USA counties listed in the appendix that have not yet had a measles outbreak in 2019 (as of April 15) either lies adjacent to a county that has or is served by a major international airport and is thus at risk of imported measles cases resulting in a local outbreak. Besides Travis, Texas these include Maricopa, Arizona, Clayton Georgia, Honolulu, Hawaii, Wayne, Michigan, Salt Lake, Utah, Hennepin, Minnesota, Suffolk, Massachusetts, Loudon, Virginia, San Diego, California, and multiple counties in Florida. These counties should be targeted for enhanced surveillance and enhanced vaccination efforts.

Lastly, using the proposed analysis, we can specify the set of countries that contribute most to measles risk across the USA. The top countries ordered by risk posed are: Ukraine, Mexico, Cuba, Israel, Japan, Thailand, and Philippines. Surveillance should also be directed towards those counties with the high incoming passenger volume from these countries. Additionally, we should consider measures to improve public health in these countries— for instance, foundations that are committed to global health enhancement could allocate funding for vaccination efforts in these countries. Perhaps the most important implication of our results (appendix) is to suggest enhanced surveillance in counties such as Cook, Illinois, and Los Angeles, California, which have each so far only reported one case of measles in 2019 but, because of the presence of major international airports, could serve as the fulcrum of continuous importation of the measles virus into the USA.

We have done a separate analysis using this model for measles outbreaks in the USA between 2011 and 2018 with similarly consistent outcomes (appendix).

The focus of these analyses has been on measles because of the surge of outbreaks in the USA and globally in 2019. The analysis can be straightforwardly extended to other vaccine-preventable diseases, especially those for which NME rates and air travel are relevant to disease spread. In recent years, the most important vaccine-preventable disease that has returned to the USA is pertussis and it has already been shown that outbreaks are spatially associated with high NME rates.<sup>11</sup> We plan to analyse this case and others (eg, mumps and rubella) in the near future.

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