(ii) quantification of orthopoxvirus-specific $CD8^+$ T cells (95% sensitivity, 97% specificity) and (iii) monkeypox B21R peptide ELISA (50–100% sensitivity, 85–100% specificity, depending on the peptide and vaccination status of the subject). Taking into account that we also showed 100% concordance with CDC-confirmed monkeypox cases, it is unclear why these validated and independent approaches would be considered 'minimal' evidence.

Our colleagues also pointed out that five vaccinated individuals developed demonstrable monkeypox disease, conflicting with our hypothesis of substantial vaccine-derived protection. It is clear that antibody is both necessary and sufficient for protection against monkeypox[2] and presumably for smallpox as well[3,4]. We previously showed that immunological memory could be demonstrated for up to 75 years after smallpox vaccination[5]. Based on comparing our studies to historical data relating humoral immunity to protection against smallpox[6], we predicted that approximately one-half of vaccinated individuals in the United States would be fully protected against orthopoxvirus infection and the other one-half would probably have at least partial protection. After the monkeypox outbreak of 2003, we found that three of eight (that is, nearly one-half) of previously vaccinated subjects were fully protected against monkeypox, whereas five of eight showed partial protection, as evidenced by significantly fewer pox lesions[5] ($P = 0.045$; **Supplementary Note** online) and the observation that the most severe and life-threatening cases of monkeypox occurred in unvaccinated individuals. Similar anecdotal findings[7] described an unvaccinated mother who had ~200 monkeypox lesions, and her unvaccinated 6-year-old daughter had ~90 monkeypox lesions (in addition to encephalitis resulting in a coma lasting 12 d), whereas the previously vaccinated father developed just 2 monkeypox lesions and experienced only mild, flu-like symptoms for ~48 h.

Our colleagues noted that the B21R protein of monkeypox is present in other orthopoxviruses including those causing cowpox and smallpox. Although the B21R-specific ELISA represents only one of three distinct assays used to diagnose monkeypox infection, we would like to clarify a few points on cross-reactivity. Monkeypox B21R peptides represent a first-generation diagnostic tool that worked well for our initial studies because smallpox is extinct in nature and vaccinia (which is B21R negative) is the only cross-reactive orthopoxvirus found in the United States that is known to infect humans. We are currently testing the utility of B21R (and other candidate gene products) for developing a second generation of diagnostic reagents capable of differential diagnosis between monkeypox and smallpox. These viruses have large and complex genomes that have been sequenced and are ready to be fully characterized. With this genomic knowledge in hand, this is an appropriate time to develop orthopoxvirus-specific diagnostics.

In conclusion, we stand by our original results that: (i) we have identified previously vaccinated individuals with full protective immunity against monkeypox infection, (ii) we have developed a series of independent diagnostic techniques that are highly effective at diagnosing clinically apparent and inapparent monkeypox infection, and (iii) the US monkeypox outbreak was larger than previously believed because of the identification of atypical cases of monkeypox that would not be identified using current epidemiological criteria and diagnostic techniques such as PCR that are not amenable to retrospective outbreak surveillance.

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Will travel restrictions control the international spread of pandemic influenza?

A key question in contingency planning for a possible influenza pandemic is the value of restricting international travel to and from affected countries or regions, or imposing entry or exit screening of passengers at airports[1]. The potential for infectious diseases to spread rapidly through an increasingly well-connected, steadily growing world population[2–5] was brought into sharp focus during the 2003 epidemic of severe acute respiratory syndrome (SARS). By 12 March, 150 suspected cases had been reported in seven countries. By the end of the outbreak, 27 countries had reported 8,096 suspected cases[6] and five incidents of transmission on commercial aircraft[7]. The World Health Organization (WHO) issued several travel advisories in an attempt to slow the international spread of the disease[8]. These were controversial because of their adverse economic impact and the uncertainty about their effectiveness. Here we analyze the impact of WHO travel advisories in 2003, and evaluate the likely effect of similar interventions in the case of an influenza pandemic.

The direct effect of the 2003 WHO travel advisories is difficult to quantify. There were small reductions in airline passenger numbers at the start of the epidemic, followed by larger reductions as the epidemic grew (**Fig. 1a**). Reduced international travel continued well beyond the time when WHO travel advisories were lifted. Despite markedly fewer airline passengers, cases continued to be exported throughout the epidemic, although in decreasing numbers (**Fig. 1b**).

Case isolation was highly effective in reducing onward transmission of SARS, and most imported cases were contained at their destination[6] because infectiousness peaked well after the onset of clinical symptoms. In contrast, considerable infectiousness can be associated with presymptomatic or mildly symptomatic influenza infection[5,9]. Secondary influenza infections would be more likely to arise on international flights and from imported cases, accelerating international spread well beyond that seen for SARS. Conversely, the incubation period of influenza is short compared with SARS (~1.5 d[10,11] rather than 4 d[12]), which reduces the probability an asymptomatic person will travel. This effect, however, is more than offset by the much faster epidemic growth

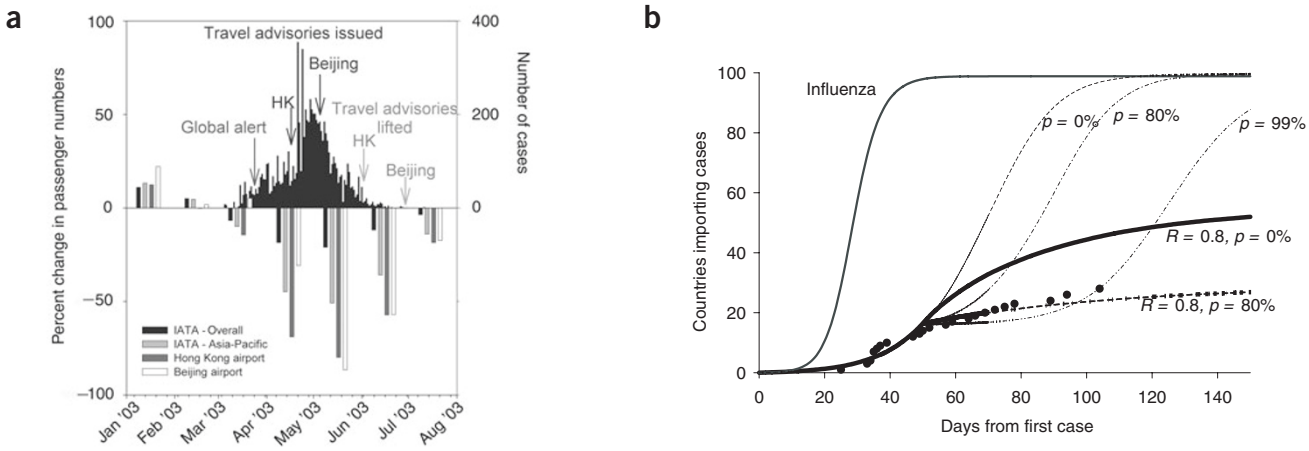

Figure 1 International travel and epidemic spread. (**a**) Daily SARS case numbers in 2003 (thin black bars)[13] and monthly percentage change (over previous year) in airline passenger volume (thicker bars). Four air passenger datasets are shown: global passengers (black)[14], Asia-Pacific passengers (light gray)[14], Hong Kong airport passengers (dark gray)[15] and Beijing International Airport passengers (white)[16]. (**b**) Timeseries of the average number of countries importing cases from a source country within a SARS epidemic, as calculated from a mathematical model of epidemic spread within a set of 100 countries connected by airline travel (**Supplementary Note**); 1,000 model simulations were performed. *p* represents the proportion by which travel is reduced at the start of the epidemic. Assuming source control fails (that is, uncontrolled spread in source country), the impact of 0% (dashed line), 80% (dash-dot line) and 99% (dash-dot-dot line) reductions in travel are shown. Control of the source epidemic (represented by the reproduction number, *R*, falling to 0.8 on day 50) is shown for $p = 0\%$ (heavy solid line) and $p = 80\%$ (heavy dashed line). The number of countries having reported SARS cases is plotted by onset date of first case (dots; day 50 was 12 March 2003)[6]. The predicted rate of spread of an influenza pandemic (with no interventions) is also shown (gray line)[13].

rate for pandemic influenza—potentially an average doubling time as short as 2.3 d (compared with 5.8 d for SARS; **Fig. 1b** and **Supplementary Note** online).

To examine the impact of travel restrictions more rigorously, we constructed a simple mathematical model of an epidemic in a source country with cases exported to any of 100 other countries with equal probability. As a best-case scenario, we assume exported cases do not seed new epidemics and exit screening is 100% effective, so only asymptomatic cases are exported (**Supplementary Note**). Travel restrictions reduce the probability of any individual leaving an outbreak area, and so reduce the rate at which non-source countries import cases (**Fig. 1b**). However, travel reductions of the order of 80%, for example, only increase the interval between exports by days (**Supplementary Note**). Travel restrictions with >99% effectiveness are needed to increase the time between exports to the order of weeks (**Supplementary Note**). Even at this level, travel restrictions only slow the exportation of cases rather than halting spread (**Fig. 1b**). Compliance with travel advisories and effectiveness of screening are major issues in implementing such a stringent policy.

Key to the impact of travel reductions is the rate of growth of the epidemic in the source country and its eventual final scale. If the source epidemic is controlled before there are thousands of cases (bringing the number of secondary cases per infected individual, *R*, to below 1) travel restrictions during the containment phase may have a large impact on the probability that an infected individual travels out of the source area and potentially seeds a new outbreak (**Fig. 1b**). Early intervention in the source region is crucial: containment of a pandemic influenza strain is probably only feasible when there are less than 50 cases[11].

The effect of airline travel on international spread of infection is complicated by heterogeneities in the airline network[3–5]. If only a partial restriction of air travel is possible, closure of highly connected hub airports has the potential to slow (but not halt) the epidemic more effectively than a homogenous reduction in global air travel[4]. But these heterogeneities only have a major role when global case numbers are low: once there are tens or hundreds of thousands of cases and multiple epidemics, travel restrictions have little impact even if optimally targeted.

Governments will use several methods to try to reduce the risk to their own population in the event of an emerging epidemic in another country, including travel advisories, passenger screening or even rigorously enforced border restrictions. Our analysis of SARS in 2003 strongly suggests that the issued travel advisories (along with individuals' perception of risk) induced large reductions in travel, but that these were too late (after the effective implementation of internal control strategies) and of too small a magnitude to impact the global spread of SARS had there not been such effective control of the epidemics within affected areas. Our analysis also indicates that restrictions on travel will be of limited benefit in slowing global spread of a pandemic influenza outbreak that is not contained at its source. There may be a role for travel restrictions applied to the source country while containment efforts are underway—minimizing the chance that one of the first few hundred infections of an outbreak might be exported to a region where containment would be less feasible.

Country-based contingency plans for the next influenza A pandemic should therefore largely focus resources on facilitating treatment, monitoring and control of new cases at home. Once case numbers exceed a few hundred in source areas, only rapidly implemented and almost total restriction of international travel can prevent the export of cases and the triggering of new epidemics in unaffected areas. The efforts of the WHO and the international community should be targeted at bringing any emerging influenza epidemic under control as rapidly as possible in the country in which the new strain first emerges. Success in this task is likely to be the dominant factor in restricting international spread.

Note: Supplementary information is available on the Nature Medicine website.

ACKNOWLEDGMENTS

We gratefully acknowledge funding from the European Union (to T.D.H., N.M.F., R.M.A.), the Wellcome Trust (to T.D.H., R.M.A.) and the Medical Research Council (N.M.F.) We also thank the referees for their comments.

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