

of the intermediate T-T<sup>-</sup> after the first C-C bond breakage, T<sup>-</sup> after the second C-C cleavage, and the final product of repaired base T. The various dissections are shown in Fig. 3, D, F, and H, and fig. S4. Thus, we obtained the ultrafast electron hopping of FET3 in 6, 11, and 15 ps and the electron return after repair in 437, 2890, and 819 ps for AnPL, DmPL, and AtPL, respectively. Knowing the total QYs (Fig. 1C), we can also derive the second C-C cleavage in 87, 48, and 36 ps and the futile back electron transfer BET2 in 1138, 149, and 527 ps, respectively, for three PLs (table S1).

To recapitulate, we have identified 10 elementary steps in the repair reaction by DNA photolyase, including 7 ET steps, and measured their time scales in real time (table S1). Consequently, we can calculate the QY of each step that contributes to the total QY (table S2). In Fig. 4, A and B, we show the two resolved photocycles for class I AnPL and class II AtPL, respectively, with the corresponding reaction times of each step. For class I PL (Fig. 4A), the two systems we studied, AnPL and EcPL, show a dominant tunneling pathway with the highest QYs (table S2). For class II PL (Fig. 4B), the two systems studied here, DmPL and AtPL, adopt mainly a two-step hopping route, also with good repair efficiency. For other PLs [class III CcPL and ssDNA-specific AtPL (AtCRY3)], both tunneling and hopping channels are operative (table S1). These detailed dynamics and time scales for seven ET reactions involved in repair can be used to derive microscopic pictures of various reorganization energies; their relevant reduction potentials; and, thus, reaction driving forces (table S3) (21, 24, 25). We did not observe clear evidence for the possible flickering resonance for the initial electron bifurcation, as proposed recently in a theoretical study (26).

Figure 4C shows the repair QYs along the evolutionary path from the microbial class I to the eukaryotic class II PLs, with initial electron bifurcation into the tunneling route FET2 and the hopping path FET1 and their resulting QYs (QY2 and QY1). Clearly, the tunneling route in class I leads to a higher repair QY. With the decrease in the rates of tunneling, the hopping channel comes to dominate in class II PLs. Consequently, class II PLs can never reach the class I repair QY because the electron path at Ade<sup>-</sup> also bifurcates into the repair channel to the CPD and the futile path back to the original ground state, both of which share similar hopping rates. The conserved active-site configuration and the folded flavin structure that occur as a result of evolution in the entire photolyase-cryptochrome superfamily (11–15, 27–30) are essential to ensure a unified electron-transfer mechanism through electron path bifurcation into two operative routes for all CPD photolyases.

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## SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/354/6309/209/suppl/DC1  
Materials and Methods  
Figs. S1 to S4  
Tables S1 to S4  
References (31–36)

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## INFLUENZA

# Role for migratory wild birds in the global spread of avian influenza H5N8

## The Global Consortium for H5N8 and Related Influenza Viruses\*†

Avian influenza viruses affect both poultry production and public health. A subtype H5N8 (clade 2.3.4.4) virus, following an outbreak in poultry in South Korea in January 2014, rapidly spread worldwide in 2014–2015. Our analysis of H5N8 viral sequences, epidemiological investigations, waterfowl migration, and poultry trade showed that long-distance migratory birds can play a major role in the global spread of avian influenza viruses. Further, we found that the hemagglutinin of clade 2.3.4.4 virus was remarkably promiscuous, creating reassortants with multiple neuraminidase subtypes. Improving our understanding of the circumpolar circulation of avian influenza viruses in migratory waterfowl will help to provide early warning of threats from avian influenza to poultry, and potentially human, health.

**I**n 2014, highly pathogenic avian influenza (HPAI) virus of the subtype H5N8 caused disease outbreaks in poultry in Asia, Europe, and North America (1–3). Avian influenza viruses are a threat both to global poultry production and to public health; they have the potential to cause severe disease in people and to adapt to transmit efficiently in human populations (4). This was the first time since 2005 that a single subtype of HPAI virus had spread over such a large geographical area and the first time that a Eurasian HPAI virus had spread to

North America. The rapid global spread of HPAI H5N8 virus outbreaks raised the question of the routes by which the virus had been transmitted.

The segment encoding for the hemagglutinin (HA) surface protein of the HPAI H5N8 viruses is a descendant of the HPAI H5N1 virus (A/Goose/Guangdong/1/1996), first detected in China in 1996 (5). Since then, HPAI H5N1 viruses have become endemic in poultry populations in several countries. The H5 viruses have developed new characteristics by mutation and by reassortment with other avian influenza (AI) viruses, both in poultry and in wild birds. In 2005–2006, HPAI H5N1 spread from Asia to Europe, the Middle East, and Africa during the course of a few months. Although virus spread traditionally had been

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attributed to transport of infected poultry, infected poultry products, or HPAI-virus-contaminated materials, several observations in the 2005–2006 epidemic suggested that wild birds also might have carried the virus to previously unaffected areas (6).

A HPAI H5N8 virus with genes from viruses of the influenza A (H5N1) A/Goose/Guangdong/1/1996 lineage was first detected in birds at live bird markets in China in 2010 (7). This HPAI H5N8 virus was a reassortant virus with the HA gene segment from HPAI H5N1 virus and other gene segments from multiple other AI viruses circulating in eastern China (7) and is now categorized as HPAI H5 virus clade 2.3.4.4 (7). This clade is unusually promiscuous and has been found in combination with six different neuraminidase (NA) segments, and multiple H5Nx viruses may be circulating at the same time and in the same region (8, 9). The propensity of HPAI H5 virus clade 2.3.4.4 to form novel subtypes capable of rapid, global spread is a major concern.

HPAI H5N8 virus caused a large avian influenza outbreak in poultry in South Korea in the winter of 2013–2014 and subsequently spread to Japan, North America, and Europe, causing outbreaks there between autumn 2014 and spring 2015 (table S1). However, it is not clear by which routes HPAI H5N8 virus spread so rapidly around the world. Although there have been reports on parts of these outbreaks (1, 2, 10) and speculation on possible routes of transmission (3), no comprehensive global analysis has yet been performed.

The goal of this study was to analyze the available genetic, epidemiological, and ornithological data for evidence of the relative contributions from poultry trade and from wild bird movements (3, 6) for the global spread of clade 2.3.4.4 during 2014–2015. For this purpose, we performed phylogeographic analysis of HPAI H5N8 viruses detected in wild birds and poultry from this global outbreak. In addition, we analyzed migration patterns of wild birds found infected with HPAI H5N8 virus, epidemiological investigations of HPAI H5N8 virus outbreaks, and poultry-trade records from countries where HPAI H5N8 virus was reported (11).

Initial phylogenetic analysis was performed using HA sequences from HPAI H5 clade 2.3.4.4 viruses of poultry and wild birds from around the world between 2004 and 2015, including subtypes H5N1, H5N2, H5N3, H5N5, H5N6, and H5N8. From 2004 to 2012, clade 2.3.4.4 viruses were circulating predominantly in Eastern Asia (China), with some transmission to Southeastern Asia (Fig. 1 and fig. S1). During this period, transmission involving domestic anseriformes (ducks and geese) appears to dominate, although some contribution from domestic galliformes (chickens and turkeys) and short-distance migratory wild birds (e.g., mallard ducks) is also evident (Fig. 1). Unlike H5 segments from other clades, which are mostly found as H5N1, the HPAI H5 segment of the clade 2.3.4.4 viruses reassorts frequently, acquiring NA segments from cocirculating low pathogenic avian influenza (LPAI) subtypes, including N5 (from 2006 to 2010), N2

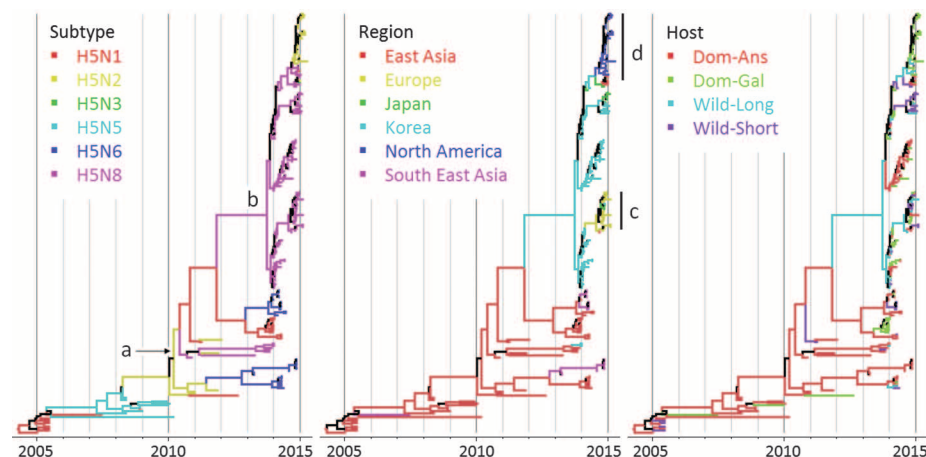
(from 2008 to 2012), N8 (from 2010), and, more recently, N6 (from 2013) (8). To indicate the host species and regions in which the reassortments are thought to have occurred, a reassortment measure was calculated using the number of branches in the posterior set of phylogenetic trees for which the NA subtype changed while the host species and region traits remained the same (normalized by branch lengths). This measure suggests that most of the observed reassortants were generated in domestic anseriformes (fig. S2), and particularly domestic anseriformes in Eastern Asia (China) within the time period 2004 to 2012 (fig. S3).

The time to the most recent common ancestor (TMRCA) for the HA segment of all clade 2.3.4.4 HPAI H5N8 sequences was estimated as June 2010 [95% highest posterior density (HPD), January to October 2010]; the TMRCA for the corresponding NA segments was similar (September 2010; 95% HPD, April to December 2010). Clade 2.3.4.4 HA H5N8 sequences were found in two subclades (Fig. 1). The smaller and earlier subclade (a in Fig. 1) contained the first sequenced 2.3.4.4 HPAI H5N8 virus [A/Duck/Jiangsu/ki203/2010 (H5N8)]. The larger and more recent subclade (b in Fig. 1) contained sequences from outbreaks in South Korea and other countries included in this study and caused multiple HPAI outbreaks in 2014 and 2015 globally. The TMRCA of subclade b was September 2013 for both HA (95% HPD, July to November 2013) and NA (95% HPD, May to November 2013). Consistent with earlier findings (1, 10), the phylogeny indicates that HPAI H5N8 was introduced into South Korea by long-distance migrant wild birds that acquired it from the pool of HPAI H5 viruses circulating in domestic anseriformes in Eastern Asia (China), although we

formally cannot exclude the possibility that HPAI H5 viruses were circulating in unsampled locations (Fig. 1).

Distinct, well-supported clades were identified in South Korea, likely originating in the transmission of HPAI H5N8 viruses from long-distance migrants to other wild and domestic birds (10). One clade (c in Fig. 1) was ancestral to the European outbreak and another (d in Fig. 1) was ancestral to the North American outbreak. Again, we cannot exclude the possibility that viruses from these subclades were present in unsampled locations.

More detailed phylogenetic analyses, using only clade 2.3.4.4 H5N8 HA sequences with location coordinates (11), showed that the virus spread along two main long-distance migration routes: one from the east Asia coast/Korean peninsula, north to the Arctic coast of the Eurasian continent, then west to Europe; and the other north from the Korean peninsula, then east across the Bering Strait, and south along the northwest coast of the North American continent to Canada and the United States (Fig. 2 and movie S1). The reconstruction did not indicate any spread between Europe and North America. The TMRCA for European HA segments was August 2014 (95% HPD, July to October 2014), and September to October 2014 (95% HPD, August to November 2014) for the North American HA segments (table S2, a and b). Similar results were found from analysis of the NA segments (table S2, c and d). There were also four separate introductions into Japan, the first estimated around February 2014 (ancestral date of single virus A/Chicken/Kumamoto/1-7/2014), and then three more, all with TMRCA in October and November 2014. The sequences from one Japanese introduction were most closely related to sequences from Taiwan and those from



**Fig. 1. Maximum clade credibility (MCC) time-scaled phylogenetic tree of multisubtype HA sequences colored by subtype, region, and host-type traits.** The clades marked a and b contain H5N8 sequences, and c and d contain sequences from Europe and North America, respectively. The displayed MCC tree was obtained from a posterior set of trees inferred using the Bayesian Evolutionary Analysis Sampling Trees (BEAST) program (13) with the SRD06 nucleotide substitution model, uncorrelated relaxed clock model, and constant population size tree prior. The branches are colored according to the most probable ancestral trait, and ancestral traits were inferred by a symmetric (subtype and region) or asymmetric discrete trait model (host-type) upon the posterior tree set (14). Host types are Dom-Ans (red), domestic anseriform birds; Dom-Gal (green), domestic galliform birds; Wild-Long (blue), long-distance migratory wild birds; Wild-Short (purple), short-distance migratory wild birds.

another introduction to the Russian (A/Wigeon/Sakha/1/2014) and European sequences.

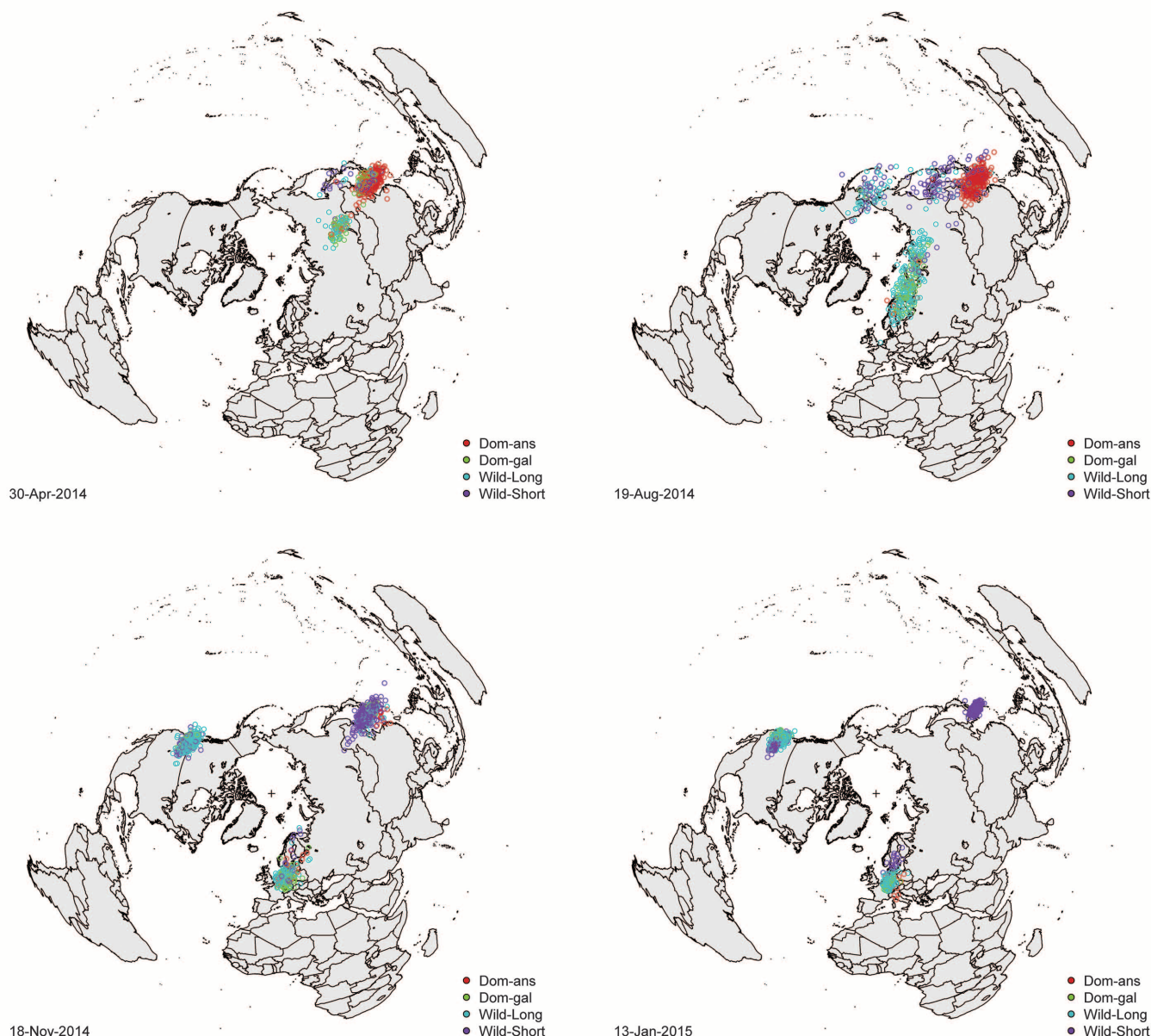
The phylogenetic data were also used to infer the ancestral host categories of the most recent common ancestor of the European and North American outbreak sequences, thus providing evidence for which host type had introduced the viruses into those areas (Fig. 3, figs. S4 and S5, and table S2). The most likely ancestral host category for the North American outbreak for both HA and NA segments was long-distance migrants (HA, 66%; NA, 84%). A similar result was obtained for Europe (HA, 66%; NA, 70%).

Several wild bird species with known HPAI H5N8 sequences were long-distance migrants at different stages of their migratory cycle, depending on time and place found (table S3): Five of the nine species found in South Korea in winter 2013–2014 were long-distance migrants at their wintering sites or on spring migration. Both in North America and Europe, two of the four species found in winter 2014–2015 were long-distance migrants at their wintering sites or on autumn migration (17) (tables S4 and S5 and fig. S6).

The April 2014 HPAI H5N8 virus outbreak in Japan had different characteristics from the later

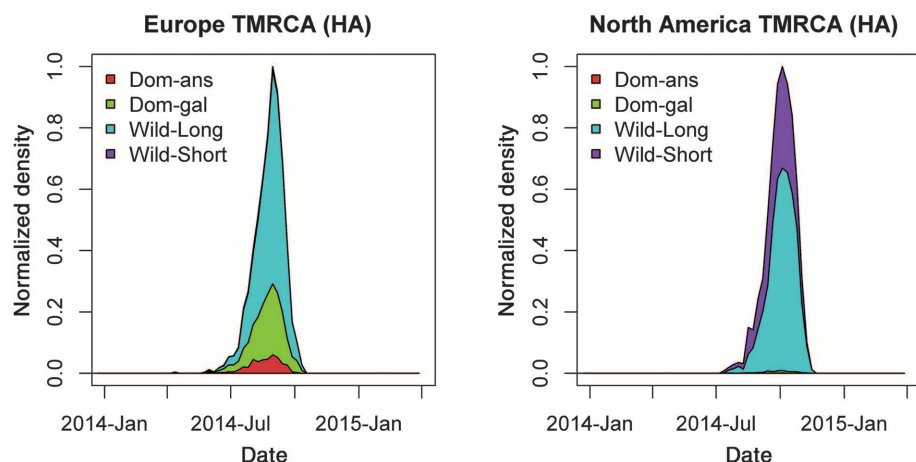
outbreaks in North America and Europe. The Japan outbreak was the only one that was contemporaneous with the outbreak in South Korea, and no wild birds were found positive for HPAI H5N8 virus in Japan during that outbreak.

Qualitative analysis of data from outbreak investigations on affected poultry farms in North America, Europe, and Japan (17) (table S6) showed that the likelihood of virus introduction via contaminated water, feed, and poultry was negligible (Germany). Furthermore, no links between the outbreaks in one country and those in other countries could be attributed to personnel contacts or



**Fig. 2. Reconstruction of the transmission routes using phylogenetic data only from H5N8 HA sequences.** At each time slice, the host-type and location coordinates on the branches of the posterior set of phylogenetic trees are inferred and plotted as a cloud of points. The host type was inferred by discrete trait model (as Fig. 1) (14), and the continuous location coordinates were inferred using a homogeneous Brownian motion diffusion model (15). The map projection used is the azimuthal equal areas projection, centered on the North Pole, which is marked with a + sign. Color key as for Fig. 1; see also movie S1.





**Fig. 3. Posterior distributions of TMRCA of HA sequences from Europe and North America with H5N8 subtype only, including host-type reconstructions, based upon a posterior set of phylogenetic trees generated as in Fig. 1. Color key as for Fig. 1.**

trade of live animals, feed, or products of animal origin (Germany, Netherlands, United Kingdom, and Hungary). Many affected poultry farms were located in areas where wild waterfowl are abundant (Germany, Netherlands, United Kingdom, Italy, and Canada). Direct contact with infected wild birds (United States) or indirect contact with materials (e.g., bedding material, boots, and wheels of vehicles) contaminated with wild-bird feces was considered the most likely route of introduction into poultry holdings (United States, Germany, Netherlands, United Kingdom, and Italy). In some outbreaks, the source of infection was unknown or inconclusive (Japan and Hungary).

We reviewed data from the Food and Agriculture Organization of the United Nations (FAO) (12) for 2011 to 2013 on export and import of live domestic ducks and chickens of affected countries to estimate the risk of spread of HPAI virus from South Korea to other countries via the international poultry trade (table S7). Data on the export of live poultry from North Korea and Mongolia, also in East Asia, were not available from FAO. Although all countries (Japan, Canada, United States, Germany, Netherlands, United Kingdom, Italy, and Hungary) where HPAI H5N8 virus emerged between November 2014 and February 2015 imported live chickens and live domestic ducks in 2013, South Korea reported the export of a low number of live chickens and no export of live domestic ducks, although unreported cross-border trade cannot be excluded. Nevertheless, based on these data, it seems unlikely that international trade in live poultry played a major role in the long-distance spread of South Korean clade HPAI H5N8 virus in 2014–2015.

Our analysis, using four different sources of data, indicates that the main routes of large-scale geographical spread of HPAI H5N8 virus were most probably via long-distance flights of infected migratory wild birds, first in spring 2014 from South Korea or other unsampled locations in the

region to northern breeding grounds and then in autumn 2014 from these breeding grounds along migration routes to wintering sites in North America and Europe.

Recognition of a likely role of wild birds in the spread of HPAI reinforces the need to improve biosecurity on poultry farms and to exclude wild birds from the immediate vicinity of poultry farms. Culling wild birds and draining or disinfecting wetlands would not be effective because these viruses disseminate on rapid time scales over very large distances, making reactive interventions of this kind impractical and ineffective, as well as contravening commitments made by signatory countries to the Convention on Migratory Species and the Ramsar Convention on Wetlands.

The potential role of wild birds in the circumpolar circulation of influenza viruses does point to the need to increase our knowledge about the connectedness at the vast circumpolar (sub)arctic breeding areas between migratory waterfowl populations originating from different wintering areas. Surveillance of waterfowl at the crossroads of migratory flyways to wintering areas in Europe, Asia, and North America would inform epidemiological risk analysis and provide early warning of specific HPAI threats to poultry, and potentially human, health.

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#### SUPPLEMENTARY MATERIALS

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Materials and Methods

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## POLITICAL SCIENCE

# How economic, humanitarian, and religious concerns shape European attitudes toward asylum seekers

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What types of asylum seekers are Europeans willing to accept? We conducted a conjoint experiment asking 18,000 eligible voters in 15 European countries to evaluate 180,000 profiles of asylum seekers that randomly varied on nine attributes. Asylum seekers who have higher employability, have more consistent asylum testimonies and severe vulnerabilities, and are Christian rather than Muslim received the greatest public support. These results suggest that public preferences over asylum seekers are shaped by sociotropical evaluations of their potential economic contributions, humanitarian concerns about the deservingness of their claims, and anti-Muslim bias. These preferences are similar across respondents of different ages, education levels, incomes, and political ideologies, as well as across the surveyed countries. This public consensus on what types of asylum seekers to accept has important implications for theory and policy.

Europe currently faces the largest refugee crisis since the Second World War. In 2015, Europe received ~1.3 million new asylum claims (1), and many more people are expected to flee to Europe as conflicts in the Middle East and other regions linger on. The number of migrants trying to reach Europe via the Mediterranean Sea who have been reported missing or dead totaled 3771 in 2015 alone (2), and this number is likely to be higher in 2016 as asylum seekers embark on new and even more dangerous routes to Europe after the implementation of the refugee deal between the European Union and Turkey (3).

As more and more people flee war-torn countries and persecution, refugee-receiving democracies must confront a fundamental challenge: how to

honor international commitments—including treaties like the United Nations 1951 Refugee Convention—to process asylum claims and provide shelter to accepted refugees, while at the same time developing asylum policies that are supported by domestic voters.

There is considerable heterogeneity in the exposure of European countries to the asylum crisis (Fig. 1). Whereas some countries, like Germany and Sweden, process a large number of asylum applications per capita, others, like the United Kingdom and Czech Republic, share a comparatively small responsibility. Yet the migrant crisis has been so severe that it has resulted in political conflict and social tensions widely across Europe, including extreme right-wing parties mobilizing citizens around asylum issues (4), frequent arson attacks on asylum centers (5), and the partial closing of Schengen borders.

As the crisis threatens national solidarity, the social contract, and continental unity, European policy-makers face increasing public pressure to find policy solutions. Although public preferences may not always directly translate into policies, a sizable political science literature has shown that, in democratic countries, particularly salient

and high-profile public policies often respond markedly to public opinion (6–8). In the context of this study, a case in point is the recent “Brexit” referendum in the United Kingdom in which the public voted for the United Kingdom to exit the European Union, a decision that has been attributed to rising anti-immigrant backlash in the United Kingdom (9). And whereas public opinion is a crucial factor, a key problem for both academic scholars and policy-makers alike is a lack of knowledge as to why some native-born citizens oppose and others support the welcoming of particular asylum seekers.

A large literature has examined public attitudes toward immigrants (10), ethnic minorities (11), and Muslims (12, 13) in general, but far fewer studies have looked at attitudes toward asylum seekers (14–21). The latter studies have provided important insights into the correlates of anti-asylum seeker sentiment, but either they are limited to particular countries or they rely on observational data from standard survey questions that ask about asylum seekers in general and do not use experiments to differentiate between different types of asylum seekers (22). Furthermore, they have mostly been conducted before the current asylum crisis. There still exists very little systematic and experimental evidence to inform the heated ongoing political debates over asylum policies with the voice of European voters. In particular, we lack a comprehensive assessment that captures which particular types of asylum seekers the European public is willing to accept given the current crisis.

To provide such an assessment, we designed a conjoint experiment and embedded it in a large-scale online public opinion survey that we fielded in 15 European countries (23). We used entropy balancing (24) to reweight our sample data to match the demographic margins from the populations of each country. Details about the sample, design, and statistical analysis can be found in the supplementary materials (SM) (25). All analyses, except otherwise noted, were prespecified in a preregistered analysis plan made available at the Political Science Registered Studies Dataverse (<http://dx.doi.org/10.7910/DVN/YUNKUL>).

Conjoint experiments ask subjects to evaluate hypothetical profiles with multiple, randomly varied attributes and are widely used in marketing and, increasingly, in other social science fields to measure preferences and the relative importance

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