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Systemic resilience to cross-border infectious disease threat events in Europe

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Abstract

Recurrent health emergencies threaten global health security. International Health Regulations (IHR) aim to prevent, detect and respond to such threats, through increase in national public health core capacities, but whether IHR core capacity implementation is necessary and sufficient has been contested. With a longitudinal study we relate changes in national IHR core capacities to changes in cross-border infectious disease threat events (IDTE) between 2010 and 2016, collected through epidemic intelligence at the European Centre for Disease Prevention and Control (ECDC). By combining all IHR core capacities into one composite measure we found that a 10% increase in the mean of this composite IHR core capacity to be associated with a 19% decrease (p = 0.017) in the incidence of cross-border IDTE in the EU. With respect to specific IHR core capacities, an individual increase in national legislation, policy & financing; coordination and communication with relevant sectors; surveillance; response; preparedness; risk communication; human resource capacity; or laboratory capacity was associated with a significant decrease in cross-border IDTE incidence. In contrast, our analysis showed that IHR core capacities relating to point-of-entry, zoonotic events or food safety were not associated with IDTE in the EU. Due to high internal correlations between core capacities, we conducted a principal component analysis which confirmed a 20% decrease in risk of IDTE for every 10% increase in the core capacity score (95% CI: 0.73, 0.88). Globally (EU excluded), a 10% increase in the mean of all IHR core capacities combined was associated with a 14% decrease (p = 0.077) in cross-border IDTE incidence. We provide quantitative evidence that improvements in IHR core capacities at country-level are associated with fewer cross-border IDTE in the EU, which may also hold true for other parts of the world.

KEYWORDS

epidemic, infectious diseases, International Health Regulations, outbreak, pandemic, threat events

1 | INTRODUCTION

Global health security has been undermined by infectious disease threat events (IDTE) such as severe acute respiratory syndrome (SARS) during 2002–2003, pandemic influenza A (H1N1) in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, Ebola virus disease in 2014, and Zika virus infection during 2015–2016 (Dzau, Fuster, Frazer, & Snair, 2017; Morens, Folkers, & Fauci, 2008; Paules & Fauci, 2017). These IDTE have caused substantial human suffering, placed considerable pressure on government resources, and inflicted significant economic damage. In financial terms, the cost of potential pandemics can amount to US$60 billion per year (Sands, Mundaca-Shah, & Dzau, 2016; Sands, Turabi, Saynisch, & Dzau, 2016). However, if mortality costs are also taken into account, the annual cost can be as high as US$490 billion (Fan, Summers, & Jamison, 2016).

To prevent, protect against, control and provide a public health response to the international spread of disease, the World Health Organization (WHO) led efforts to update the International Health Regulations (IHR), and the updated regulations were adopted in 2005 and came into force in 2007 (Gostin, DeBartolo, & Friedman, 2015; World Health Organisation, 2005). The aim was to prepare 'States Parties' to be able to detect and respond to these threats more quickly and effectively. To prevent Public Health Emergencies of International Concern (PHEIC) that can be a threat to global health security, the IHR oblige all 'States Parties' to establish IHR core capacities (Table 1) to detect, assess, notify and report events, and to respond to public health risks and emergencies.

However, the persistent occurrence of IDTE post IHR implementation has raised questions about the implementation, compliance, and enforcement of these measures (Commission on a Global Health Risk Framework for the Future, 2016; Gostin et al., 2015; Gostin, DeBartolo, & Katz, 2017; Hoffman, 2014; Suthar, Allen, Cifuentes, Dye, & Nagata, 2018; World Health Organisation, 2015) since self-reported compliance with IHR can mask deficiencies. A review of IHR core capacities during the 2009 influenza A (H1N1) pandemic documented an inadequate response to the emergency (World Health Organisation, 2011), an assessment of the 2014 Ebola outbreak highlighted slow reaction and poor communication (World Health Organisation, 2016), while the 2016 Zika virus outbreak highlighted the need for efficient surveillance. Although these post hoc assessments of failures in public health responses to IDTE can help to identify deficiencies in IHR core capacities and IHR non-compliance, additional factors might be responsible for the emergence of IDTE (Gostin et al., 2015, 2017). It is possible that IHR core capacities are necessary but not sufficient to prevent the spread, control or response to such threats. They might not comprehensively identify and mitigate all the underlying drivers and determinants of IDTE in an increasingly interconnected and interdependent world (Glaesser, Kester, Paulose, Alizadeh, & Valentin, 2017; Jones et al., 2008; Morens et al., 2008; Paules & Fauci, 2017; Semenza, Lindgren, et al., 2016; Semenza, Rocklov, Penttinen, & Lindgren, 2016; Weiss & McMichael, 2004). For example, measles has recently resurfaced

TABLE 1 International health regulations core capacities

Core capacity 1: National legislation, policy & financing • Legislation, laws, regulations, administrative requirements, policies or other government instruments in place for implementation of IHR • Available and accessible funding for implementing IHR NFP functions and IHR core capacity strengthening
Core capacity 2: Coordination and NFP communications • A functional mechanism for the coordination of relevant sectors in the implementation of IHR • IHR NFP functions and operations in place as defined by the IHR (2005)
Core capacity 3: Surveillance • Indicator based surveillance, including an early warning function for the timely detection of a public health event • Event based surveillance established and functioning
Core capacity 4: Response • Public health emergency response mechanisms established and functioning • Case management procedures implemented for IHR relevant hazards • Infection prevention and control established and functioning at national and hospital levels • A programme for disinfection, decontamination and vector control established and functioning
Core capacity 5: Preparedness • A Multi-hazard National Public Health Emergency Preparedness and Response Plan developed and implemented • Priority public health risks and resources mapped and utilized
Core capacity 6: Risk communication • Mechanisms for effective risk communication during a public health emergency established and functioning
Core capacity 7: Human resource capacity • Human resources available to implement IHR core capacity requirements
Core capacity 8: Laboratory • Coordinating mechanism for laboratory services established • Laboratory services available to test for priority health threats • Influenza surveillance established • Laboratory biosafety and laboratory biosecurity (Biorisk management) practices in place and implemented • Laboratory data management and reporting established
Points of entry • General obligations at PoE fulfilled (including for coordination and communication) • Routine capacities and effective surveillance established at PoE • Effective response at PoE established
IHR Potential hazard 1: zoonotic events • Mechanisms for detecting and responding to zoonoses and potential zoonoses established and functional
IHR Potential hazard 2: food safety • Mechanisms established and functioning for detecting and responding to foodborne disease and food contamination

Note: Since IHR potential hazards 3 (chemical events) and IHR potential hazards 4 (radiation emergencies) do not directly relate to IDTE they were not included in this analysis.
IHR: International Health Regulations; NFP: National Focal Point; PoE: Points of Entry.

Source: http://apps.who.int/iris/bitstream/10665/84933/1/WHO_HSE_GCR_2013.2_eng.pdf?ua=1 in Europe as a result of global resurgence, increasing mobility and low vaccine uptake, in part related to vaccine hesitancy (Leong, 2018; Massad, 2018). In 2017, the chikungunya virus was introduced into France and Italy by viraemic passengers and spread by *Aedes albopictus* mosquitoes, in part due to favourable climatic conditions (Lillepold, Rocklov, Liu-Helmersson, Sewe, & Semenza, 2019; Rezza, 2018; Rocklöv et al., 2019; Semenza & Suk, 2018).

International donors invested US$0.88 billion in outbreak preparedness, response and management of cross-border externalities in 2013 (Schaferhoff et al., 2015) and national governments have allocated substantial resources to IHR core capacity implementation. Despite this global public health effort, no quantitative assessment of the effectiveness of IHR core capacity implementation on cross-border IDTE has been conducted to date. We designed a panel study to investigate the association between improvements in national IHR core capacities with changes in cross-border IDTE, using epidemic intelligence data collected by the European Centre for Disease Prevention and Control (ECDC) and, specifically, whether IHR core capacities accurately reflect the ability of countries to prevent the spread of IDTE. We assessed country-level IHR core capacity implementation against the occurrence of cross-border IDTE from 2010 to 2016 using a longitudinal modelling framework controlling for population size.

2 | METHODS

2.1 | Epidemic intelligence

The ECDC is an EU agency with a mission to monitor, identify (early warning and assessment) and respond to serious cross-border health threats. (The European Parliament & the Council of the European Union, 2013) This is analogous to the World Health Organization (WHO) IHR, where countries are also committed to further build their capacities to detect, assess and notify, and report on public health emergencies of international concern. Thus, the cross-border IDTE we analyse here lend themselves to an analysis of IHR core capacities.

European Centre for Disease Prevention and Control conducts epidemic intelligence, a process of systematic collection and collation of information on threats from health from a variety of sources. Cross-border IDTE are assessed and verified to ensure they correspond to real public health events (for examples of IDTE see (Semenza, Lindgren, et al., 2016; Semenza, Rocklov, et al., 2016)). The assessment is based on an analysis, using IHR and Early Warning and Response System (EWRS) criteria and expert opinion (Table S1). ECDC initiated data collection for epidemic intelligence in June 2005. We analysed cross-border IDTE that originated in one of the 28 EU Member States (EU28) from 2010 to 2016. This time period included the migrant wave of 2015 (Semenza, Carrillo-Santisteve, et al., 2016). We included IDTE with a risk of introduction to or propagation between Member States within the EU/EEA and IDTE that may require timely and coordinated EU action to contain (Table S1). We also analysed cross-border IDTE for other parts of the world that were recorded by ECDC epidemic intelligence, despite the low numbers of IDTE identified in those countries. We excluded travel-associated Legionnaires' disease outbreaks not originating in the EU28 from the analysis due to changes in reporting during the study period.

2.2 | Core capacities

WHO has developed an analytical framework for monitoring the achievement of IHR core capacities (World Health Organisation, 2013). It allows country data for each core capacity, PoE and potential hazards to be analysed in detail (Table 1) (World Health Organisation, 2011). The main purpose of the framework is to enable countries to measure their current status and assess progress over time. Although individual IHR core capacities do not necessarily carry the same weight in an assessment of capabilities, all attributes are given the same weight in the framework. The scores range from 0% to 100% and were available from 2010 to 2016 (World Health Organisation). The analysis also included potential hazard 1 (zoonotic events) and potential hazard 2 (food safety); however, potential hazard 3 (chemical events) and potential hazard 4 (radiation emergencies) were not included in this analysis as they do not relate directly to IDTE.

2.3 | Statistical analysis

We determined the incidence of cross-border IDTE per capita in different countries based on the annual number of IDTE in a country divided by the annual population of the country. We modelled the relative change in the incidence of cross-border IDTE that originated in one country of the EU28, with a panel study, using a longitudinal general estimation equation framework (GEE) (Hanley, Negassa, Edwardes, & Forrester, 2003) with a Poisson log-link using random effects by country of origin to adjust for unmeasured confounders. We used an exchangeable correlation structure of the observations within countries, not to make prior assumptions of the temporal covariance structure. Initially, we performed univariate analysis of the association of each of the IHR core capacities to cross-border IDTE. The annual population estimates for countries were included in the model as an offset variable, providing a denominator for the capita rate of IDTE. We used R 3.4 (Anonymous, 2014) and SAS 9.4 (the PROC GENMOD procedure) statistical softwares for data management and analysis. We present estimates of incidence rate of cross-border IDTE for a 10% increase in each IHR core capacity (scale: 0%–100%). For the combined contribution of different IHR core capacities, it was not possible to perform a multivariate regression, due to high internal correlations. Instead, we conducted analysis of a composite indicator of the mean core capacity and additionally ran a principal component analysis for the 11 capacities (Table 1). The principal component analysis (PCA) reduced the dimensionality of the IHR core capacities by making linear combinations and can be used instead of studying individual capacities, for example, in situations of collinearity. The component scores were normalized in order to be comparable to the original core component scales (0%–100%) in the univariate analysis. We performed the same Poisson regression analysis using the PCA scores as predictor variables of the risk for cross-border IDTE, to study the combined effect of core capacities.

3 | RESULTS

A total of 135 cross-border IDTE in the EU28 met the study inclusion criteria between 2010 and 2016 (Tables 2; S1). Over the study period, the composite measure of the IHR core capacities, which averages 11 capacities (Table 2; Figure 1) in the EU28 increased by 14 percentage points and reached 83% by 2016. IHR core capacities are highly correlated with each other and with GDP (Table S2). However, GDP was not associated with IDTE incidence rates (incidence rate ratio (IRR) = 1.00; 95% CI: 0.99–1.00; $p = 0.439$).

We present both the IHR core capacity effect as a composite metric (using principal component analysis instead of multivariate analysis due to the high inter-core capacity correlations) and the univariate analysis of each IHR core capacity individually and the composite mean core capacities, adjusting for population size, temporal correlation and country.

In a longitudinal (or panel) study, a 10% increase in the mean IHR core capacity as a composite metric, the unadjusted IRR was 0.81 with a 95% confidence interval (95% CI) of 0.68–0.96. This corresponds to a 19% decrease in the relative risk for cross-border IDTE for every 10% increase in the mean IHR core capacity (Table 3; Figure 1). Figure 1 overlays the number of cross-border IDTE and the composite measure of the IHR core capacities in the EU28.

Analysis of IDTE in other parts of the world (besides EU28) was constrained by few cross-border IDTE detected in these countries and reported to ECDC. Nevertheless, a 10% increase in the mean of all IHR core capacities combined was associated with a 14% decrease ($p = 0.077$) in the incidence of cross-border IDTE in countries other than the EU28. Due to sample size constraints, a regional analysis was not possible. The results for specific IHR core capacities for all non-EU countries combined is provided in the Supporting Information (Table S3).

TABLE 2 Infectious disease threat events and IHR core capacities, Europe, 2010–2016

		IHR Core capacities				
Year	IDTE	Min	Mean	Median	Max	*N*
2010	30	34.00	69.24	70.25	96.56	28
2011	30	46.50	73.10	73.90	96.56	28
2012	25	44.56	76.97	80.10	96.80	28
2013	11	52.60	80.10	81.70	97.20	28
2014	15	60.30	81.59	81.35	99.60	28
2015	17	55.89	82.07	84.45	99.56	28
2016	7	64.60	83.35	85.81	99.56	28
All	135	34.00	78.06	79.35	99.60	196

Note: Data for the 28 member states of the European Union.
IDTE: Infectious disease threat events; IHR: International Health Regulations.

With respect to the association of a 10% increase in individual core capacities with the incidence of cross-border IDTE in the EU28, core capacity 1 (national legislation, policy and financing) was associated with a 10% decrease (95% CI: 0.84, 0.98) in the incidence of cross-border IDTE (Figure 2); core capacity 2 (coordination and National Focal Point communications) with a 12% decrease (95% CI: 0.80, 96); core capacity 3 (surveillance) with a 19% decrease (95% CI: 0.66, 0.99); core capacity 4 (response) with a 21% decrease (95% CI: 0.71, 0.89); core capacity 5 (preparedness) with a 10% decrease (95% CI: 0.84, 0.97); core capacity 6 (risk communication) with a 12% decrease (95% CI: 0.78, 0.97); core capacity 7 (human resource capacity) with a 10% decrease (95% CI: 0.84, 0.97); core capacity 8 (laboratory) with a 23% decrease (95% CI: 0.70, 0.85). In our analysis, IHR core capacity at PoE was not protective (0.007% decrease; 95% CI: 0.96, 1.03). IHR core capacity for potential hazard 1 (zoonotic events) was not associated with cross-border IDTE (5% decrease; 95% CI: 0.81, 1.10); the same was found for potential hazard 2 (food safety) (4% increase; 95% CI: 0.80, 1.35) (Table 3; Figure 2). A bivariate analysis adjusted for GDP per capita yielded essentially the same point estimates (Table S4).

The principal component analysis revealed that three components explained the majority of variability of the IHR core capacities (Table S5). However, only the first PCA score was significantly related to IDTE with an estimated 20% decrease in risk for every 10% increase in the core capacity score (95% CI: 0.73, 0.88). The individual core capacity weights related to this component was in line with the univariate analysis by relating mainly to IHR core capacities and less so to hazards. The IRR estimate from the first PCA score was also very similar to the estimate from the average composite measure of the IHR core capacities (decrease 20% vs. 19%), and further indicated that the IRR from the univariate analysis of IHR core capacities cannot be combined, due to the strong inter-core capacity correlations.

4 | DISCUSSION

Our longitudinal study links improvements in IHR core capacities over time with a reduction in incidence of cross-border IDTE in Europe. This temporal association indicates that IHR core capacities are necessary and sufficient to prevent, detect and respond to cross-border IDTE and thus contribute to health security. This analysis of EU data indicates that IHR core capacities capture relevant public health measures for the prevention of cross-border IDTE and that improvement in these core capacities is associated with a reduction in the incidence of cross-border IDTE. Strengthening IHR core capacities could further counteract the emergence and re-emergence of cross-border IDTE in Europe. Our analysis indicate that these conclusions can also be applied to other parts of the world, although our

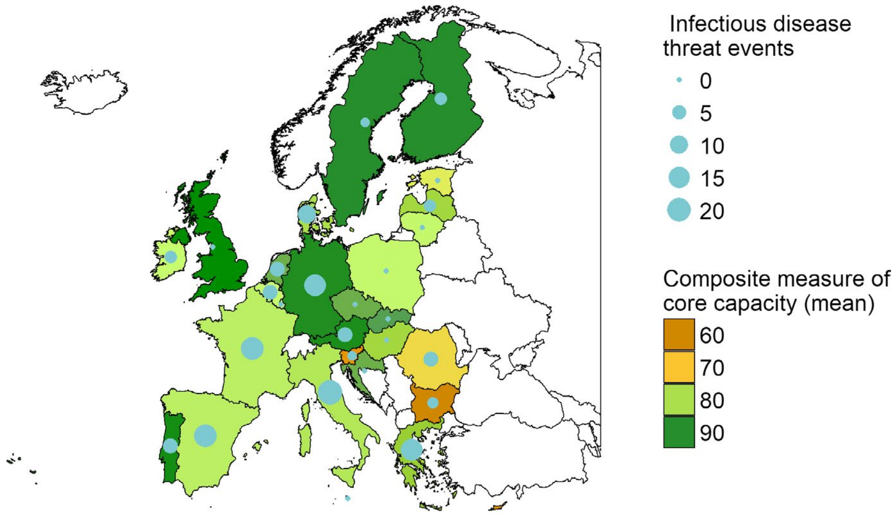

FIGURE 1 Composite measure (mean) of IHR core capacities with infectious disease threat events in Europe, 2010–2016 [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Association of IHR core capacities with infectious disease threat events, Europe, 2010–2016

IHR core capacity	IRR	IRR 95% CI Lower	IRR 95% CI Upper	*p*-value
Composite measure (mean)	0.806	0.675	0.962	0.017
Core capacity 1: National legislation, policy & financing	0.903	0.836	0.975	0.009
Core capacity 2: Coordination and NFP communications	0.879	0.801	0.963	0.006
Core capacity 3: Surveillance	0.811	0.665	0.991	0.040
Core capacity 4: Response	0.790	0.706	0.885	<0.001
Core capacity 5: Preparedness	0.903	0.838	0.972	0.007
Core capacity 6: Risk communication	0.875	0.780	0.970	0.011
Core capacity 7: Human resource capacity	0.901	0.835	0.973	0.008
Core capacity 8: Laboratory	0.771	0.696	0.854	<0.001
Points of Entry	0.993	0.960	1.027	0.688
IHR Potential hazard 1: zoonotic events	0.946	0.813	1.101	0.475
IHR Potential hazard 2: food safety	1.040	0.802	1.347	0.769

Note: Data for the 28 member states of the European Union.
Unadjusted univariate analysis (not adjusted for GPD).
CI: 95% confidence interval; IRR: Incidence rate ratio.

sample size of cross-border IDTE outside the EU28 was somewhat limited due to reduced sensitivity of ECDC's epidemic intelligence there (Table S1,S3).

National legislation, policy and financing (core capacity 1) and coordination and NFP communications (core capacity 2) were both associated with fewer cross-border IDTE. 'State Parties' are required to integrate IHR core capacities into national health systems including procedures related to notification, risk assessment, collaboration and international response coordination (Kluge et al., 2018; Suthar et al., 2018). Developing resilient health systems relies not only on

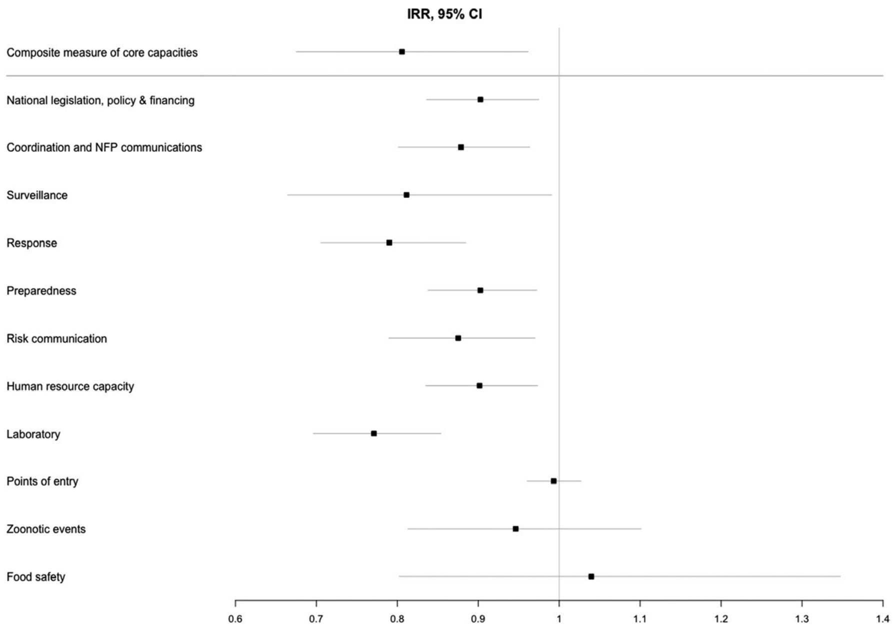

FIGURE 2 Forest plot of unadjusted univariate analysis of the association of IHR core capacities with infectious disease threat events, Europe, 2010–2016. Note: Composite measure of core capacities: mean of IHR core capacities IRR: Incidence rate ratio; 95% CI: 95% confidence interval

strengthening health security efforts but also effective delivery of health care services and access to vaccines, diagnostics, medicines and insurance coverage prior to, during and after a cross-border IDTE.

Surveillance (core capacity 3) is vital for early detection, rapid risk assessment, notification and response to epidemic events, in order to intercept the development of a full-blown cross-border IDTE (Balajee, Arthur, & Mounts, 2016; Lindgren, Andersson, Suk, Sudre, & Semenza, 2012; Wolicki et al., 2016). To this end, surveillance needs to be flexible and sensitive and to encompass syndromic, laboratory-based, population-based and sentinel systems (Wolicki et al., 2016). In our analysis, national surveillance was associated with fewer IDTE, presumably because they were intercepted prior to international spread.

Response (core capacity 4) was highly significant in our analysis. Systemic resilience to IDTE entails management and coordination of operations to rapidly respond to epidemic events that could develop into public health emergencies of national or international concern. It also includes active case management, infection control and decontamination, the importance of which were demonstrated during the MERS-CoV and Ebola outbreaks in 2012 and 2014, respectively (Siedner, Gostin, Cranmer, & Kraemer, 2015; Zaki, Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012).

In our analysis, preparedness (core capacity 5) was also protective for cross-border ITDE. It includes developing public health emergency response plans, standard operating procedures (SOPs) and emergency operation centres (EOCs) and ensuring the availability of resources such as stocks of vaccines. For example, IDTE associated with influenza, such as the avian influenza A (H5N1) outbreaks and the 2009 influenza A (H1N1) pandemic, have created the need to stockpile vaccines. Advancing preparedness measures can increase the systemic resilience against IDTE. For example, the Ebola outbreak in Nigeria in 2014 was quickly detected and contained, in part due to adherence to public health emergency management (PHEM) principles (Frieden & Damon, 2015; Shuaib et al., 2014).

Risk communication (core capacity 6) focuses on the dissemination of information to the public about the health risks of a cross-border IDTE. It needs to be tailored to the social, religious, cultural, political and economic profile of the affected population and to promote appropriate prevention and control interventions as our analysis indicates.

Strengthening the skills and competencies of public health personnel (core capacity 7) is critical for surveillance and an effective response to cross-border IDTE.(Balajee et al., 2016; Wolicki et al., 2016) Having a trained epidemiologic workforce enables risk assessments to be translated rapidly into public health interventions in order to avert a full-blown cross-border IDTE.

Laboratory services (core capacity 8) are central to the early detection, investigation and response to epidemic events (prior to the spread of a cross-border IDTE) and this capacity was highly significant in our analysis. Laboratory capacity for outbreaks requires effective diagnostics, quality assurance, sample referral, biosafety and laboratory management systems (Albiger, Revez, Leitmeyer, & Struelens, 2018). Timely laboratory identification and cooperative sharing of infectious agents must occur through national or collaborating centres (Gostin et al., 2017).

We did not find IHR capacities for PoE and potential hazards (zoonotic events and food safety) to be associated with fewer cross-border IDTE. However, animal health and livestock practices have played a role in Q-fever outbreaks in the Netherlands and Germany, and the *E. coli* O157 outbreak in the United Kingdom. Food safety is another potential driver of cross-border IDTE and farming, processing, handling, preparation and storage practices have been implicated in multi-country hepatitis A, salmonella and Norovirus outbreaks.

4.1 | Limitations

The use of country-level IHR core capacities can result in ecological fallacies. Heterogeneity in the data or historic events could have biased our results. For example, improved infectious disease prevention in general during the study period (improvements in vaccination coverage, food safety, water supply, etc.) could have confounded our results. While GDP (as a broad proxy for general prevention) was highly correlated with IHR core capacities, GDP was not associated with IDTE incidence rates in our analysis. Moreover, we have no indication of improvements in general prevention over the study period; to the contrary, vaccination coverage for example, has declined in certain countries (e.g. Italy). It is important to bear in mind that this longitudinal study has a much stronger plausibility of an inference of a causal association than a simple cross-sectional study. We relate a change in IHR core capacities to a change in IDTE over time. Thus, due to this temporal association, the causal inference is high, but nevertheless potentially subject to biases. Another potential bias is reporting bias due to the self-assessment of IHR core capacities (Gostin et al., 2017) which could have shifted our results to the null. Selective reporting could also have contributed to the high inter-core capacity correlations, which decreases the granularity of our results. To overcome this lack of objective metrics, WHO has introduced a Joint External Evaluation (JEE) as part of the IHR Monitoring and Evaluation Framework (Bell et al., 2017; World Health Organisation, 2019a). This is a voluntary, multi-sectoral, peer-to-peer process with external experts to assess country capacity to prevent, detect and rapidly respond to public health risks. Such an assessment is likely to be more objective than a self-assessment of IHR core capacities. As of April 2019, 82 countries had conducted a JEE, but only five of these countries were EU Member States (Belgium, Finland, Latvia, Lithuania and Slovenia) (World Health Organisation, 2019b). Once all EU28 countries have completed a JEE, analysis of the association with IDTE will need to be revisited.

5 | CONCLUSION

Our analysis links IHR core capacity implementation with health security in Europe and other parts of the world. This association is important in view of competing demands for limited public health resources that pitches preparedness planning versus other dire public health needs. Advancing pandemic preparedness and response, upgrading public health systems, and research and development in low- and middle-income countries is projected to cost $4.5 billion per year (Sands, Mundaca-Shah, et al., 2016). Our analysis suggests that IHR core capacities capture the foundations of preparedness and that IHR deficiencies are therefore operational rather than structural. In 2014, the IHR Review Committee highlighted the need to: strengthen self-assessment; test capacities through simulations; promote regional and cross-regional learning; and measure performance through peer-review and external assessments (World Health Organisation, 2015). Our study can guide preparedness measures in Europe and elsewhere for the prevention of IDTE as, ultimately, health security depends on transparent implementation of IHR core capacities and shared accountability in an interconnected and interdependent world. IHR core capacity implementation can advance systemic resilience to cross-border IDTE in Europe.

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CONFLICT OF INTEREST

No conflict of interest.

AUTHOR CONTRIBUTIONS

JCS conceived the study, developed the study design, led the data analysis and data interpretation, and wrote the manuscript. MOS conducted the analysis and contributed to the writing. EL contributed to the writing. SB, KKA and TM collected epidemic intelligence data. JR led the data analysis and contributed to the writing of the manuscript. All authors reviewed and approved the final manuscript.

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REFERENCES

Anonymous, (2014). R core team r: A language and environment for statistical computing. R foundation for statistical computing, Vienna, Austria. Available from: http://www.R-project.org/.

Albiger, B., Revez, J., Leitmeyer, K. C., & Struelens, M. J. (2018). Networking of public health microbiology laboratories bolsters europe's defenses against infectious diseases. *Frontiers in Public Health*, *6*, 46. https://doi.org/10.3389/fpubh.2018.00046

Balajee, S. A., Arthur, R., & Mounts, A. W. (2016). Global health security: Building capacities for early event detection, epidemiologic workforce, and laboratory response. *Health Security*, *14*, 424–432. https://doi.org/10.1089/hs.2015.0062

Bell, E., Tappero, J. W., Ijaz, K., Bartee, M., Fernandez, J., Burris, H., … Jafari, H. (2017). Joint external evaluation—Development and scale-up of global multisectoral health capacity evaluation process. *Emerging Infectious Diseases*, *23*, S33-S39. https://doi.org/10.3201/eid2313.170949.

Commission on a Global Health Risk Framework for the Future. (2016). The neglected dimension of global security – a framework to counter infectious disease crises Available from: https://www.nap.edu/catalog/21891/the-neglected-dimension-of-global-security-a-framework-to-counter.

Dzau, V., Fuster, V., Frazer, J., & Snair, M. (2017). Investing in global health for our future. *The New England Journal of Medicine*, *377*, 1292–1296. https://doi.org/10.1056/NEJMsr1707974

Fan, V., Summers, L., & Jamison, D. (2016). *The iclusive cost of pandemic influenza risk*. Cambridge, MA: The National Bureau of Economic Research.

Frieden, T. R., & Damon, I. K. (2015). Ebola in west africa–cdc's role in epidemic detection, control, and prevention. *Emerging Infectious Diseases*, *21*, 1897–1905. https://doi.org/10.3201/eid2111.150949

Glaesser, D., Kester, J., Paulose, H., Alizadeh, A., & Valentin, B. (2017). Global travel patterns: An overview. *Journal of Travel, medicine*, 1-5. https://doi.org/10.1093/jtm/tax007

Gostin, L. O., DeBartolo, M. C., & Friedman, E. A. (2015). The international health regulations 10 years on: The governing framework for global health security. *Lancet (London, England)*, *386*, 2222–2226. https://doi.org/10.1016/S0140-6736(15)00948-4

Gostin, L. O., DeBartolo, M. C., & Katz, R. (2017). The global health law trilogy: Towards a safer, healthier, and fairer world. *Lancet (London, England)*, *390*, 1918–1926. https://doi.org/10.1016/S0140-6736(17)31261-8

Hanley, J. A., Negassa, A., Edwardes, M. D., & Forrester, J. E. (2003). Statistical analysis of correlated data using generalized estimating equations: An orientation. *American Journal of Epidemiology*, *157*, 364–375. https://doi.org/10.1093/aje/kwf215

Hoffman, J. J. (2014). *Making the international health regulations matter: Promoting universal compliance through effective dispute resolution*. Oxford: Routledge.

Jones, K. E., Patel, N. G., Levy, M. A., Storeygard, A., Balk, D., Gittleman, J. L., & Daszak, P. (2008). Global trends in emerging infectious diseases. *Nature*, *451*, 990–993. https://doi.org/10.1038/nature06536

Kluge, H., Martín-Moreno, J. M., Emiroglu, N., Rodier, G., Kelley, E., Vujnovic, M., & Permanand, G. (2018). Strengthening global health security by embedding the international health regulations requirements into national health systems. *BMJ Global Health*, *3*, e000656. https://doi.org/10.1136/bmjgh-2017-000656

Leong, W. Y. (2018). Measles cases hit record high in europe in 2018. *Journal of Travel Medicine*, 1-2. https://doi.org/10.1093/jtm/tay080

Lillepold, K., Rocklov, J., Liu-Helmersson, J., Sewe, M., & Semenza, J. C. (2019). More arboviral disease outbreaks in continental europe due to the warming climate? *Journal of Travel Medicine*. 1-3. https://doi.org/10.1093/jtm/taz017

Lindgren, E., Andersson, Y., Suk, J. E., Sudre, B., & Semenza, J. C. (2012). Public health. Monitoring eu emerging infectious disease risk due to climate change. *Science (New York, NY)*, *336*, 418–419.

Massad, E. (2018). Measles and human movement in europe. *Journal of Travel Medicine*, 25. https://doi.org/10.1093/jtm/tay091

Morens, D. M., Folkers, G. K., & Fauci, A. S. (2008). Emerging infections: A perpetual challenge. *The Lancet Infectious Diseases*, *8*, 710–719. https://doi.org/10.1016/S1473-3099(08)70256-1

Paules, C. I., & Fauci, A. S. (2017). Emerging and reemerging infectious diseases: The dichotomy between acute outbreaks and chronic endemicity. *JAMA*, *317*, 691–692. https://doi.org/10.1001/jama.2016.21079

Rezza, G. (2018). Chikungunya is back in italy: 2007–2017. *Journal of Travel Medicine*, *25*, 2007–2017. https://doi.org/10.1093/jtm/tay004

Rocklöv, J., Tozan, Y., Ramadona, A., Sewe, M., Sudre, B., Garrido, J., ... Semenza, J. C. (2019). Using big data to monitor the introduction and spread of chikungunya, Europe. *Emerging Infectious Diseases*, *25*(in press). https://doi.org/10.3201/eid2506.180138

Sands, P., El Turabi, A., Saynisch, P. A., & Dzau, V. J. (2016). Assessment of economic vulnerability to infectious disease crises. *Lancet (London, England)*, *388*, 2443–2448.

Sands, P., Mundaca-Shah, C., & Dzau, V. J. (2016). The neglected dimension of global security–a framework for countering infectious-disease crises. *The New England Journal of Medicine*, *374*, 1281–1287. https://doi.org/10.1056/NEJMsr1600236

Schaferhoff, M., Fewer, S., Kraus, J., Richter, E., Summers, L. H., Sundewall, J., ... Jamison, D. T. (2015). How much donor financing for health is channelled to global versus country-specific aid functions? *Lancet (London, England)*, *386*, 2436–2441. https://doi.org/10.1016/S0140-6736(15)61161-8

Semenza, J. C., Carrillo-Santisteve, P., Zeller, H., Sandgren, A., van der Werf, M. J., Severi, E., ... Kramarz, P. (2016). Public health needs of migrants, refugees and asylum seekers in europe, 2015: Infectious disease aspects. *European Journal of Public Health*, *26*, 372–373.

Semenza, J. C., Lindgren, E., Balkanyi, L., Espinosa, L., Almqvist, M. S., Penttinen, P., & Rocklöv, J. (2016). Determinants and drivers of infectious disease threat events in europe. *Emerging Infectious Diseases*, *22*, 581–589. https://doi.org/10.3201/eid2204

Semenza, J. C., Rocklov, J., Penttinen, P., & Lindgren, E. (2016). Observed and projected drivers of emerging infectious diseases in Europe. *Annals of the New York Academy of Sciences*, *1382*, 73–83.

Semenza, J. C., & Suk, J. E. (2018). Vector-borne diseases and climate change: a European perspective. *FEMS Microbiology Letters*, *365*, 1-9. https://doi.org/10.1093/femsle/fnx244

Shuaib, F., Gunnala, R., Musa, E. O., Mahoney, F. J., Oguntimehin, O., Nguku, P. M., ... Centers for Disease Control and Prevention (CDC). (2014). Ebola virus disease outbreak - Nigeria, july-september 2014. *MMWR Morbidity and Mortality Weekly Report*, *63*, 867–872.

Siedner, M. J., Gostin, L. O., Cranmer, H. H., & Kraemer, J. D. (2015). Strengthening the detection of and early response to public health emergencies: Lessons from the West African ebola epidemic. *PLoS Medicine*, *12*, e1001804.

Suthar, A. B., Allen, L. G., Cifuentes, S., Dye, C., & Nagata, J. M. (2018). Lessons learnt from implementation of the international health regulations: A systematic review. *Bulletin of the World Health Organization*, *96*, 110–121e.

The European Parliament And The Council Of The European Union. (2013). Decision no 1082/2013/eu of the european parliament and of the council of 22 october 2013 on serious cross-border threats to health and repealing decision no 2119/98/ec.

Weiss, R. A., & McMichael, A. J. (2004). Social and environmental risk factors in the emergence of infectious diseases. *Nature Medicine*, *10*, S70–76.

Wolicki, S. B., Nuzzo, J. B., Blazes, D. L., Pitts, D. L., Iskander, J. K., & Tappero, J. W. (2016). Public health surveillance: At the core of the global health security agenda. *Health Security*, *14*, 185–188.

World Health Organisation. Ihr core capacity data. Available from: http://gamapserver.who.int/gho/interactive_charts/ihr/monitoring/atlas2.html?indicator=i2&filter=filter4, Europe.

World Health Organisation. (2005). The international health regulations, 2nd edition. Available from: http://www.who.int/entity/ihr/publications/9789241596664/en/index.html.

World Health Organisation. (2011). Implementation of the international health regulations (2005). Report of the review committee on the functioning of the international health regulations (2005) in relation to pandemic (h1n1) 2009. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pd.

World Health Organisation. (2013). Ihr core capacity monitoring framework: Checklist and indicators for monitoring progress in the development of ihr core capacities in states parties. Available from: http://apps.who.int/iris/bitstream/10665/84933/1/WHO_HSE_GCR_2013.2_eng.pdf?ua=1.

World Health Organisation. (2015). Implementation of the international health regulations (2005): Report of the review committee on second extensions for establishing national public health capacities and on ihr implementation: Report by the director-general. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_22Add1-en.pdf.

World Health Organisation. (2016). Implementation of the international health regulations (2005): Report of the review committee on the role of the international health regulations (2005) in the ebola outbreak and response. Report by the director-general. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_21-en.pdf.
World Health Organisation. (2019a). Ihr (2005) monitoring and evaluation framework; joint external evaluation tool (jee tool) second edition.
World Health Organisation. (2019b). Ihr monitoring & evaluation. Available from: https://extranet.who.int/spp/ihr-monitoring-evaluation/spar/133.
Zaki, A. M., van Boheemen, S., Bestebroer, T. M., Osterhaus, A. D., & Fouchier, R. A. (2012). Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *The New England Journal of Medicine*, *367*, 1814–1820. https://doi.org/10.1056/NEJMoa1211721

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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