

patients between 2002 and 2012 were identified from the latter database. Four non-dengue controls were randomly selected for each dengue patient by matching on age, sex, calendar year, and area of residence. All participants were followed up from the index dates to the diagnosis of gastrointestinal (GI) bleeding, death, or December 31, 2015. Multivariate Cox proportional hazard regression models were used to evaluate the risk of GI bleeding in different follow-up periods after dengue virus infection (<2 months, 3–12 months, >12 months), adjusting for matching factors and bleeding-related comorbidities and medications.

Results: We identified 13269 newly diagnosed dengue patients and 53076 non-dengue matched controls. The overall incidence rate of GI bleeding was 699.01 per 100,000 person-years in the dengue cohort and 412.76 per 100,000 person-years in the controls. Stratified analyses by different follow-up periods showed that dengue patients had a higher risk of GI bleeding within two months after infection (adjusted HR 23.04, 95% CI 17.29–30.69), but there was no significant association between dengue and GI bleeding between 3–12 months (adjusted HR 0.87, 95% CI 0.59–1.30) or >12 months (adjusted HR 0.90, 95% CI 0.81–1.01) after infection.

Conclusion: Dengue virus infection was associated with the risk of developing GI bleeding only within 2 months after disease onset. It seems that dengue virus infection does not increase the long-term risk of GI bleeding among infected people.

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Identifying spatial heterogeneity in vaccination coverage in Michigan from 2008–2018: Evaluating the impact of a 2015 policy change on measles risk

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Background: In 2000, endemic measles was declared eliminated in the US. However, a proliferation of anti-vaccination sentiment over the last decade has led to measles' re-emergence, with 2019 experiencing the most measles cases in the US since 1992. Rising rates of non-medical exemptions (NMEs) and low vaccination coverage in the state of Michigan prompted an administrative vaccine policy change in 2015, mandating that parents attend an in-person vaccine education session prior to obtaining a non-medical exemption waiver. Despite the enactment of this policy, Michigan experienced a large measles outbreak in 2019.

Methods and materials: This study used school-level data from the Michigan Department of Health and Human Services from 2008–2018. School addresses were geocoded in ARCGIS and up-to-date vaccination and NME waiver rates were aggregated at the school district, county, and state level for kindergarten and seventh grade, when mandatory vaccinations are assessed. Spatial lag regression models were used to assess risk factors while accounting for spatial autocorrelation.

Results: The statewide vaccine waiver rate increased from 2008–2014, reaching a high of 5.84%, which fell to 3.58% in 2015 after the enactment of Michigan's new policy. However, since 2015, waiver rates have again been steadily increasing, reaching 4.54% in 2018. Up-to-date vaccination rates among kindergarteners were consistently below herd immunity thresholds from 2009–2018.

There was significant geographic heterogeneity at the county level, where NME rates reached a high of 19.5% in 2013, corresponding to county-level vaccination coverage of 76%. While overall NME rates decreased in 2015 after the policy change, this change was heterogeneous across the state, with persistent county-level clusters of high exemption rates remaining.

Conclusion: Despite Michigan's 2015 policy change, from 2008–2018, waiver rates remained high enough to allow measles to circulate and cause outbreaks. State-wide average estimates showed a reduction in waiver rates after this policy change, yet finer-scale data at the county- and school-level show wide variability obscured by this aggregation. Recent research has shown the potential for such pockets of low vaccination coverage to contribute to disease outbreaks, and thus these clusters present a risk of continued disease transmission and future outbreaks in Michigan.

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Enhancing risk prediction of progression to severe disease during the febrile phase of dengue: A systematic review and meta-analysis

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Background: Since no effective vaccine or specific treatment for dengue exists, the early prediction of progression to severe disease plays a key role in patient triage and clinical management during the febrile phase. Without differentiating the time-course of the illness, previous systematic reviews and meta-analyses may have failed to identify early prognostic factors for progression to severe disease. This study aimed to identify the factors associated with progression to severe dengue disease, which are detectable specifically in the febrile phase.

Methods and materials: We conducted a systematic review and meta-analysis to identify prognostic factors associated with disease progression identifiable during the febrile phase. Eight medical databases including MEDLINE, EMBASE, and Web of Science were searched for studies published from January 1997 to February 2018. The relevant studies were selected and assessed by three reviewers independently with discrepancies resolved by consensus. We performed meta-analysis for factors reported in at least four studies. Meta-analysis were performed using random-effects models; heterogeneity and publication bias were also assessed.

Results: In line with the 2009 WHO guidelines, we found that vomiting, abdominal pain and tenderness, spontaneous and mucosal bleeding, and clinical fluid accumulation were clinical features associated with severe disease. In addition, we found that the presence of specific pre-existing comorbidities (diabetes mellitus, hypertension and renal disease) were associated with progression to severe disease. We also found that individuals with a lower platelet count, lower serum albumin and higher aminotransferase levels (AST or ALT), detected during the first four days of the illness, were more prone to progress to severe disease. Dengue virus serotype 2 and secondary infections were also associated with progression to severe disease.

Conclusion: This study supports the monitoring of the warning signs described in the 2009 WHO guidelines. In addition, testing for infecting serotype and monitoring platelet count, serum albumin, AST or ALT during the febrile phase of illness would improve the early prediction of severe dengue. This improvement would have major implications for the management of patients, particularly on presentation, and health care resource allocation in endemic areas.

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Supporting polio outbreak response through mathematical modelling



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Background: Whilst wild polio outbreaks are becoming a distant memory, vaccine-derived poliovirus (VDPV) outbreaks are increasing in incidence. For many countries currently experiencing VDPV outbreaks (Philippines, Ghana, Indonesia, etc.) it has been many years since polio has been observed and the optimal location of vaccination campaigns are uncertain.

Methods and materials: A mathematical model of polio spread at a province level has been developed and fitted to historical outbreaks across Africa and Asia from 2002–present day. Separate models were fitted to wild and VDPV outbreaks. Population immunity against each polio type was also been estimated from surveillance and cross-sectional data. Polio spread is estimated assuming a gravity model approach, where populous locations that are nearby have more movement between them. Other metrics such as travel time between locations are tested.

Results: Since 2002 there have been over 50 genetically distinct outbreaks across Africa and Asia where over 14 have reported more than 10 cases. The output from the model is tested using cross-validation; parameters are estimated from 90% of outbreaks to predict the trajectory of the remaining 10% from the index case to the first vaccination campaign. Using this approach we identified a moderate predictive ability of the model, which in some cases differed from the location of the outbreak response.

Conclusion: The trajectory of polio outbreaks largely follows predictive patterns of human movement and pockets of susceptibility to infection. Outputs from mathematical modelling can inform outbreak response in real time, borrowing information from historical outbreaks. This can be especially informative in settings where polio has been absent for several years and where population immunity has changed in time.

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Emergence and global spread of novel human coronavirus OC43 genotypes associated with respiratory infections



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Background: Human coronavirus OC43 (HCoV-OC43) is commonly associated with respiratory tract infections in humans, with five genetically distinct genotypes (A to E) described so far. We identified two newly emerging HCoV-OC43 genotypes and characterized their phylogenetic, spatiotemporal spread and transmission network profiles.

Methods and materials: We obtained the full-length genomes of HCoV-OC43 strains from two previously unrecognized lineages identified among patients presenting with severe upper respiratory tract symptoms in a cross-sectional molecular surveillance study in Kuala Lumpur, Malaysia, between 2012 and 2013. Phylogeographic and transmission network analyses were estimated using a suite of computational tools.

Results: Bayesian phylogenetic, recombination and comparative genomic analyses revealed two distinct clusters diverging from a genotype D-like common ancestor through recombination with a putative genotype A-like lineage in the non-structural protein (nsp) 10 gene. Signature amino acid substitutions and a glycine residue insertion at the N-terminal domain of the S1 subunit of the spike gene, among others, exhibited further distinction in a recombination pattern, to which these clusters were classified as genotypes F and G. The phylogeographic mapping of the global spike gene indicated that the genetically similar HCoV-OC43 genotypes F and G strains were potentially circulating in China, Japan, Thailand and Europe as early as the late 2000s. The transmission network construction based on the TN93 pairwise genetic distance revealed the emergence and persistence of multiple sub-epidemic clusters of the highly prevalent genotype D and its descendant genotypes F and G, which contributed to the spread of HCoV-OC43 in the region. Finally, a more consistent nomenclature system for non-recombinant and recombinant HCoV-OC43 lineages is proposed, considering genetic recombination as an important feature in HCoV evolution and classification.

Conclusion: In summary, herein we report two novel HCoV-OC43 recombinant genotypes, designated as genotypes F and G, which were identified among patients presenting with acute respiratory tract symptoms. Using observations from phylogenetic, recombination, and comparative genomic analyses on full-length genome sequences, HCoV-OC43 genotypes F and G were likely to co-circulate worldwide.

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Risk factors associated with mortality from Neonatal tetanus in district Naseerabad, Pakistan



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Background: Neonatal tetanus (NNT) is vaccine preventable disease. Study was conducted to provide magnitude and baseline information for evidence-based intervention.