nature portfolio

Peer Review File

Increasing intensity of enterovirus outbreaks projected with climate change

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

This manuscript studies the relationship between enterovirus seasonality and climate factors, and uses data on temperature projections in China to explore future changes in the magnitude of enterovirus outbreaks in this country.

I find the results interesting, in particular, those around the importance of the range of temperatures and interannual temperature variability on the seasonality.

Main comments:

1. The authors present their work as a study of the impact of climate change on the occurrence of enterovirus outbreaks (generally/globally). However, first, they focus only on the projected changes in temperature. Second, they focus only on China for the study of the projections. I think both the geographical range of the study and the fact that temperature is the only factor that is varied in the projections should be better acknowledged throughout the manuscript.

2. Other potentially important projected changes not linked to climate change (e.g. birth rates) are not considered. Can the authors please comment on those and state the limitations of their approach in this regard?

3. Previous work looking at drivers of enterovirus seasonality identified the dew point temperature as a predictor of the seasonality of enterovirus transmission. Why was the impact of relative humidity not tested in the regression analysis here? Could adding relative humidity change the projections?

4.Can the authors comment more on the differences obtained across climate models? Only the worst case scenario is presented as main result.

Reviewer #2 (Remarks to the Author):

The ms by Baker and team provides a clear overview of the relationship between transmission and several climatic factors for enteroviruses. The retrospective analysis is then extended to consider climate projections and the potential impact of (generally) wetter and warmer climate. The paper is written well, but sometimes more specific language would be preferred especially when describing the results and interpretation (see minor comments). The team have previously used similar methods on different climate sensitive diseases, eg. RSV, COVID-19. The methods are robust. More could have been written in the discussion which would help shape the paper. The discussion could be more considered.

Specific comments;
- A table of the data that are used in the analysis, and the original spatial scale for each country would be helpful. I found myself getting confused as the data are not fully described.
- Eg. EVA71 in china, at what spatial scale? And for data with finer / different spatial scale,
- Eg. What spatial & temporal scale are the Berkeley Earth data?
- Are there any issues with the data, ie. Are they confirmed cases and how confirmed, what level of under-reporting are possible, and what are the implications?
- If climate data are gridded, how is this data scaled up for province level cases data?
- Impact of schooling on transmission: I don’t follow the text where the results are described. I would expect to see improved fits to data or a description of statistics where this specific hypothesis is described, increasing the alignment of a coefficient doesn’t feel like a very standard way to assess this hypothesis.
- Some comment on outliers in the data (Figure 1) would be valuable. It feels like the outliers tell us more than those that confirm to the general trends. Eg. Why would Nevada be an outlier in the

polio data and Tibet in the EV71 data. Presumably this is something to do with connectivity? I would also value the outliers being labelled in Fig 1 B and D (even if this becomes an appendix file)
- Please include justification of why TSIR transmission output was best to model over case data
- It would be nice to see in the discussion a comment or 2 on what can be done about the increased epidemics that settings may see, what are the realistic mitigations? Are there vaccines in development? Is air-conditioning likely to mitigate transmission? How do these findings compare to other climate sensitive diseases?

Minor:
- The language used to describe results is sometimes vague and can be difficult to interpret. For example, specific variables "playing a role" (line 131) is difficult to interpret, are they simply correlated, or on the causal pathway. Related to this, are there lab data that can support the causal pathway.
- Line 108: "matching" the datasets is a non-standard way to describe the fitting a polynomial model of climate variables on transmission rates. It can create confusion to the reader on what was actually done.
- Line 115: informally the authors "ran" the models, but technically the models fitted parameters to data
- For the climate projections, it feels like it should be mentioned that Hanan has consistent high peak size for CVA16, and why this is (already hot and humid?). From other analyses of people living in hot and humid places, what is the feasibility of mitigation?
- Please include how the results obtained in Fig 4 are derived, ie. Precisely what is used from an anova, RSS?

Note: github site was not accessible to review.

Reviewer #2 (Remarks on code availability):

I am able to review code, but not accessible (private repo).

Reviewer #3 (Remarks to the Author):

In this study, authors assess how the intensity of enterovirus outbreaks may change with climate change. To do this, considering the examples of polio, EVA71 and CVA16, they first assess how the transmission rates of these viruses are affected by temperature and other variables such as school holidays, looking at US and Chinese data. They then plug in these associations into a dynamical model to predict how enterovirus outbreak dynamics might change with of climate change, considering different climate models to explore uncertainty about climate change. They find that we might expect an important rise in enterovirus outbreak sizes with climate change.

Overall, I found that this is an interesting and well written paper. However, I have one major comment/source of concern. In their model, authors implicitly assume that immunity conferred by enterovirus infection is life-long. However, I don't think that this assumption is realistic for enteroviruses as reinfections are likely common at a young age. In this context, I wonder what the impact of the assumption of life-long immunity has on the results. In particular, I'm concerned that introducing a decay of protection following infection, may affect estimates of the impact of climate change on outbreak size. I would therefore like to see a sensitivity analyses exploring the sensitivity of their estimates and forecasts to assumptions about the duration of protection following infection.

Other comments:
Figure 1A : Center of gravity usually refers to a spatial concept. Here however, it seems this corresponds to a temporal one, something along the lines of average week of case occurrence. It's not a standard terminology in this kind of analysis, so please define the concept clearly (I am not

sure it's completely adapted for a temporal concept – so consider a term that would be more intuitive in such context).
I'd put the same subtitles in Fig 1A and B-D-C.
Fig 1 B, D. I'd use the same range of x- and y-axis so it's easier to compare the different panels.
What is the blue area in Fig 1B,D?
Fig 2B: left hand side: indicate what is being plotted on y-axis.
Line 125: "based on estimates of school semester in China and Japan". Aren't data available for school semesters in these locations? If not, how are these time periods "estimated"? I don't understand what authors do to address historical data on school holidays that are not available for polio. Can't assumptions be made about the likely timing of holidays in the US at the time? Couldn't authors assume holidays at the time were roughly similar to what they are now?
Line 145: "For locations with a large seasonal temperature range and higher mean transmission, our model predicts higher order outbreaks can occur". I don't think "higher order outbreak" will be clear for all readers. Please clarify.
"For instance, the model predicts that Liaoning in northern China may experience biennial outbreaks, defined as alternating years of high and low case numbers. Our observational data suggests that biennial outbreaks occur in Liaoning; biennial outbreaks have also been observed in other enterovirus time series in other locations [14]." If that's the case, authors should show the data. Could be in Supplementary Material. The left hand side of Fig 2B shows seasonal variations over a year; but right hand side panels predicts variations over sometimes multiple years. It would be nice if authors could show variations of cases over multiple years.
In the graph, the model predicts that in some locations, outbreaks may occur only every 3 years. Are there locations consistent with such patterns.
Fig 2E: "The ratio of the schooling peak to temperature peak for locations with two annual peaks for EVA71" I don't understand what these are and how they are computed. Label in y-axis in 2E: what is "mean transmission"? What are the definitions of schooling and temperature peaks?

Reviewer #1 (Remarks to the Author):
This manuscript studies the relationship between enterovirus seasonality and climate factors, and uses data on temperature projections in China to explore future changes in the magnitude of enterovirus outbreaks in this country.

I find the results interesting, in particular, those around the importance of the range of temperatures and interannual temperature variability on the seasonality.

We thank the reviewer for taking the time to review the manuscript and for providing comments that have helped improve the manuscript.

Main comments:

1. The authors present their work as a study of the impact of climate change on the occurrence of enterovirus outbreaks (generally/globally). However, first, they focus only on the projected changes in temperature. Second, they focus only on China for the study of the projections. I think both the geographical range of the study and the fact that temperature is the only factor that is varied in the projections should be better acknowledged throughout the manuscript.

We agree with the reviewer. The reason we only explore the effect of temperature is that we do not find a significant link between transmission and other climate variables tested (specific humidity, relative humidity and precipitation – note, relative humidity was added on revision in response to the reviewer's comment below).

As the reviewer notes, the projections are focused on China. We agree it could be clearer in the text, particularly when discussing the projections. We have now updated this text.

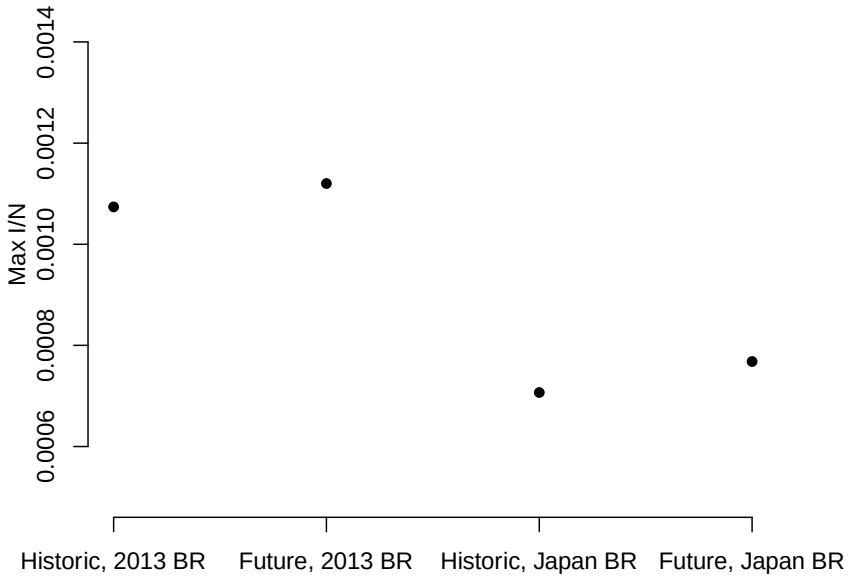
2\. Other potentially important projected changes not linked to climate change (e.g. birth rates) are not considered. Can the authors please comment on those and state the limitations of their approach in this regard?

The reviewer is correct, we do not tackle several aspects of global change that may influence disease dynamics in the future. We focus on the potential impact of climate change and we hold other factors constant. Demographic changes, such as a change in birth rates, will also impact the trajectory of enterovirus outbreaks. We could not find future projections of Chinese birth rates out to 2100 and developing these projections in beyond the scope of the manuscript. However, given the Chinese birth rate is currently declining, we perform an exercise to simulate future outbreaks using a lower birth rate.

In the figure, we take the current (2024) birth rate from Japan, a country with one of the lowest birth rates globally (Japan: 6.7/1000 population) and simulate outbreaks for Beijing given this

birth rate (the Beijing model currently uses 2013 birth rate for Beijing, 8.9/1000). We simulate epidemics using "historic" climate, "future" climate, 2013 birth rate for Beijing ("2013 BR" in the figure below) and current Japan birth rate.

As birth rates decline, the replenishment rate of the susceptible population also declines, meaning that the peak outbreak size is reduced. This reduction is greater than the increase due to climate change, however, it is important to note that this scenario is unlikely realistic as we do not account for the impact of reduced birthrates on total population size, N. As births decline over the long-run, population size will also decline, which would reduce the y-axis denominator. More detailed local-scale population and birth rate projections are required to understand the impact of these factors. Importantly, for both the Japan or Beijing birth rate, climate change acts to increase outbreak size in the future compared to the past. In fact, the relative effect of climate change is greater when the birth rate is reduced (4% mean increase in future peak size in the 2013 birth rate model compared to the past, vs 9% mean increase in the Japan birth rate model).



We have updated the discussion text and include this figure in the supplementary materials. "Demographic changes may impact future outbreaks: declining birth rates could reduce the size of the susceptible population and hence the projected epidemic peak size (Supplementary Fig. 8)."

3\. Previous work looking at drivers of enterovirus identified the dew point temperature as a predictor of the seasonality of enterovirus transmission. Why was the impact of relative humidity

not tested in the regression analysis here? Could adding relative humidity change the projections?

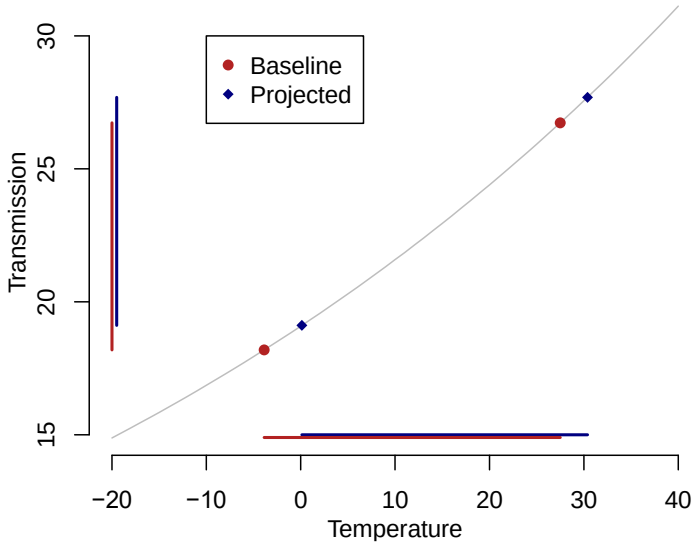
We agree with the reviewer. We now test for the role of relative humidity as a driver of transmission of EVA71 and CVA16. We do not find a significant effect of relative humidity on transmission of EVA71 and CVA16. In prior work on the climate drivers of enterovirus transmission in the USA (Pons-Salort 2018), a strong correlation is found between temperature and enterovirus transmission intensity, with dew point temperature only a marginally better predictor (AIC (dew point temperature) -1572 vs -1545 (temperature)). Our work supports this result and suggests that temperature is a primary driver of transmission.

Edited text: "We fit separate regressions (EVA71, CVA16, polio) of temperature, specific humidity, relative humidity and precipitation on log empirical transmission rates. We find a significant positive effect of temperature on transmission, though the effect of specific humidity, relative humidity and precipitation was not found to be significant (Supplementary Table 2)."

4.Can the authors comment more on the differences obtained across climate models? Only the worst case scenario is presented as main result.

There are two key factors that explain the differences across models:

1) As mentioned in the text, we find the seasonal temperature range particularly important for governing outbreak dynamics. Certain models (e.g. INM-CM4-8) project a decline in seasonal temperature range, while others (e.g. GFDL-ESM4) project an increase. Even within a model, there are province-level differences in whether the temperature range is expected to increase or decrease with climate change.
2) The nonlinear relationship between temperature and transmission means there isn't a one-to-one relationship between temperature range and transmission range. We demonstrate this in the figure below (new supplementary Fig. 7). In the figure below, the baseline temperature range is greater than the projected temperature range, but due to the nonlinear (grey line) relationship between temperature and transmission, the projected transmission range is (marginally) greater than the baseline transmission range.



Next text “An additional source of heterogeneity across climate models comes from the non-linear effect of temperature on transmission (Supplementary Fig.7). In some locations, although the seasonal range in temperature declines, the seasonal range of transmission may increase due to the estimated convex temperature-transmission curve. This effect dominates for climate models, and locations, where the projected decrease in temperature change is marginal.”

Reviewer #2 (Remarks to the Author):

The ms by Baker and team provides a clear overview of the relationship between transmission and several climatic factors for enteroviruses. The retrospective analysis is then extended to consider climate projections and the potential impact of (generally) wetter and warmer climate. The paper is written well, but sometimes more specific language would be preferred especially when describing the results and interpretation (see minor comments). The team have previously used similar methods on different climate sensitive diseases, eg. RSV, COVID-19. The methods are robust. More could have been written in the discussion which would help shape the paper. The discussion could be more considered.

We agree with the reviewer and thank them for their helpful comments and for taking the time to review the manuscript.

Specific comments;
- A table of the data that are used in the analysis, and the original spatial scale for each country would be helpful. I found myself getting confused as the data are not fully described.

- Eg. EVA71 in china, at what spatial scale? And for data with finer / different spatial scale,
- Eg. What spatial & temporal scale are the Berkeley Earth data?

- Are there any issues with the data, ie. Are they confirmed cases and how confirmed, what level of under-reporting are possible, and what are the implications?
- If climate data are gridded, how is this data scaled up for province level cases data?

We thank the reviewer for pointing out the lack of clarity over the spatial and temporal scales of the data. We have now included this table in the supplementary materials (Supplementary Table 1) and updated the text to better explain the data in both the main text and methods section.

EVA71 and CVA16 data are at the province level in China and national level in Japan. In China, the serotype-specific incidence data are calculated as the product of the weekly reports of HFMD from syndromic surveillance at the province level and the weekly prevalence of virologically-confirmed enterovirus serotypes from a subset of HFMD cases also at the province level, as derived in Takahashi et al (2016) *Plos Med*. In Japan, the serotype-specific incidence data are similarly calculated as the product of the weekly reports of HFMD per sentinel site from syndromic surveillance at the national level, the number of sentinel sites at the national level, and the weekly prevalence of virologically-confirmed enterovirus serotypes from a subset of HFMD cases also at the national level, as derived in Takahashi et al (2018) *Royal Society Interface.* Polio data is at the state level in the USA. Under-reporting is a key issue in surveillance data, and in our models we account for this by incorporating a reporting rate in the TSIR model (\rho parameter from Equation 4), which we estimate to approximately 1% for polio and 2% for CVA16 and EVA71, suggesting that infections are indeed being under-reported. This is likely due to a multitude of factors including the relatively moderate symptoms of HFMD, asymptomatic spread of polio, and its impact on healthcare-seeking behavior. ERA5 climate data are gridded at the 0.25*0.25 degree latitude and longitude level, hourly. Historic Berkeley Earth data is gridded 1*1 degree latitude and longitude, daily. Climate data are average both spatially and temporally to match the resolution of the enterovirus data. Spatial averages are calculated in the raster package in R using shapefiles delineating province or state boundaries.

New main text “All gridded climate datasets are spatially and temporally averaged to match the resolution of the disease data (for a list of data sources see Supplementary Table 1).” Methods/Data section is updated.

- Impact of schooling on transmission: I don’t follow the text where the results are described. I would expect to see improved fits to data or a description of statistics where this specific hypothesis is described, increasing the alignment of a coefficient doesn’t feel like a very standard way to assess this hypothesis.

We agree with the author. We have now included the regression results in the supplementary material for the model that includes both temperature and schooling. We find schooling to be a significant predictor of transmission.

"For EVA71 and CVA16 we find a significant effect of schooling on transmission in a regression model that includes both temperature and schooling (Supplementary Table 3)."

- Some comment on outliers in the data (Figure 1) would be valuable. It feels like the outliers tell us more than those that confirm to the general trends. Eg. Why would Nevada be an outlier in the polio data and Tibet in the EV71 data. Presumably this is something to do with connectivity? I would also value the outliers being labelled in Fig 1 B and D (even if this becomes an appendix file)

This is an interesting question. Both Tibet and Nevada are outliers in terms of their population. Although present-day Nevada is the 33rd most populous state (2020 census 3.19 million) in the 1950s when polio was circulating, Nevada was the least populous state in the USA (1950 census 160,083) apart from Alaska (1950 census 128,643) – for reference, at that time, New York was the most populated state with 14.8 million residents. Given the lower population numbers, case data from Nevada is sparse. We count 514 total cases between 1940-1960 (see pasted table below) compared to 38,192 cases in New York. The sparse time series makes it hard to assess the seasonality of the outbreak in Fig. 1. Removing Nevada from our dataset does not affect our regression results (temp co-efficient without Nevada: 0.012988, p-value = 2e-04 ***; with Nevada: 0.012914, p = 0.000206 ***).

Tibet is the least populated province in China (2022 population 3.6 million). The next most populated province is Qinghai with 5.95 million residents. The high elevation in Tibet means it is colder than other provinces of a similar latitude (see Supplementary Fig 2). Our results suggest that cold weather could reduce transmission of enteroviruses which may lead to the sparse time series and unusual seasonality in Tibet, although a smaller population also likely plays a role.

The table below shows the total cases recorded (1940 – 1960) for polio in US states. We show values for states with the eight lowest (red) and highest (green) case numbers.

State	Total Cases
NEVADA	514
DELAWARE	869
VERMONT	912
NEW HAMPSHIRE	1052
WYOMING	1267

DISTRICT OF COLUMBIA	1366
RHODE ISLAND	1630
MONTANA	1746
IOWA	13660
MINNESOTA	16671
OHIO	21963
MICHIGAN	23697
TEXAS	25781
ILLINOIS	27534
NEW YORK	38192
CALIFORNIA	38446

We have now added text "In Fig. 1C, both Nevada and Tibet appear to be outliers in terms of seasonality based on latitude. This is likely due to the sparse population numbers in these locations (Nevada was the least populous US state in 1950, apart from Alaska) making it hard to discern the seasonal trend."

- Please include justification of why TSIR transmission output was best to model over case data

From a mechanistic viewpoint, climate is expected to impact the transmission rate of a pathogen. Our TSIR approach estimates the transmission rate, \beta_t, so that we can use this as the dependent variable in our regression model. The mapping between transmission and incidence/cases is nonlinear and depends on the size of the susceptible population.

In a previous paper, we show how our TSIR approach produces unbiased estimates of the impact of climate on transmission for pathogens with long-lasting immunity (Baker et al. 2018).

We have now added text "Prior work suggests that regression climate factors on transmission, as opposed to incidence, provides an unbiased estimate of the climate effect (cite Baker 2018)'

- It would be nice to see in the discussion a comment or 2 on what can be done about the increased epidemics that settings may see, what are the realistic mitigations? Are there vaccines in development? Is air-conditioning likely to mitigate transmission? How do these findings compare to other climate sensitive diseases?

Vaccines are available for specific enterovirus serotypes, but given there are 80+ nonpolio enterovirus serotypes, a multivalent vaccine would be the most effective intervention. Although research is underway to develop a multivalent enterovirus vaccine against common serotypes that cause HFMD (Deng et al 2020), candidates are still in early phase development. Nonpharmaceutical interventions are effective at limiting enterovirus transmission (for example,

enterovirus outbreaks were disrupted during COVID19 lockdowns (Park et al. 2021)). These measures could be leveraged during periods of predicted high transmission. Developing an early warning system for enterovirus outbreaks using near-term weather forecasts could be valuable in determining when these measures should be applied.

For several climate-sensitive directly-transmitted diseases we observe more intense outbreaks patterns at high latitudes and more year-round persistent outbreaks at low latitudes. Interestingly, we note this pattern for wintertime diseases such as influenza (Baker et al. 2022) and RSV (Baker et al. 2019) as well as the summertime disease studied here. In all three of these cases, we find that the seasonal amplitude of the climate forcing (the range of temperature or range of humidity) appears to determine these latitudinal outbreak patterns. The fact that climate models vary in terms of the projections for change in this amplitude is a key area of uncertainty for these diseases in the future.

We now discuss interventions in the main text: “The proposed development of a multivalent vaccine may be one of the most promising approaches to mitigating possible intensifying outbreaks \cite{deng2020development}. Meanwhile nonpharmaceutical interventions have been shown to be effective at limiting enterovirus transmission \cite{park2021epidemiological}. These measures could be leveraged during periods of predicted high transmission.

We find that reducing uncertainty in the temperature coefficient could help improve precision of projections, but variability matters. The influence of variability speaks to a possible role for incorporating near-term climate forecasts into models to predict the intensity of present-day outbreaks. These early warning systems could then be used to target interventions. More broadly, the role of variability and uncertainty needs to be more carefully considered in future work on the impacts of climate change on infectious disease.”

Minor:
- The language used to describe results is sometimes vague and can be difficult to interpret. For example, specific variables “playing a role” (line 131) is difficult to interpret, are they simply correlated, or on the causal pathway. Related to this, are there lab data that can support the causal pathway.

We thank the reviewer – we have edited the unclear text.

Pons-Salort et al. 2018 re-analysed some older 1960s experimental data on climate and poliovirus survival. They found that dew point temperature was positively correlated with virus survival. To our knowledge, similar studies using temperature data alone have not been conducted.

- Line 108: “matching” the datasets is a non-standard way to describe the fitting a polynomial model of climate variables on transmission rates. It can create confusion to the reader on what was actually done.

We apologize. In this text we are describing the merging of the datasets (climate data and disease data), not the model fitting. The model fitting is described in the next paragraph. We have replaced matching with merging as is the technical term for the function.

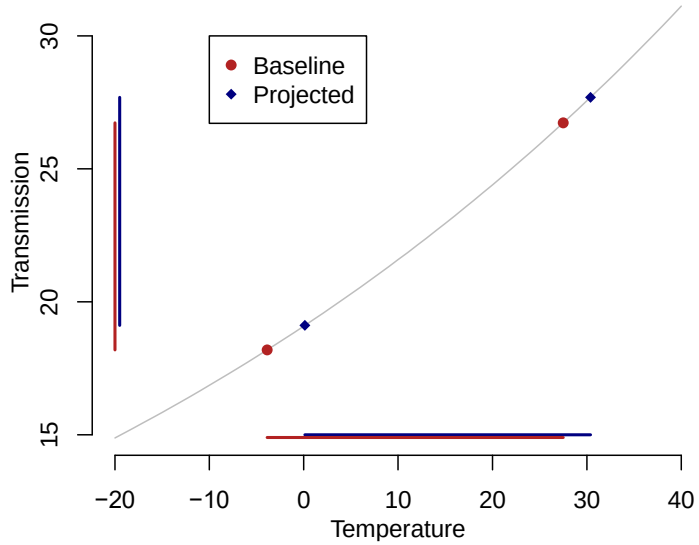
- Line 115: informally the authors “ran” the models, but technically the models fitted parameters to data

We thank the reviewer; we have replaced “ran” with “fit”.

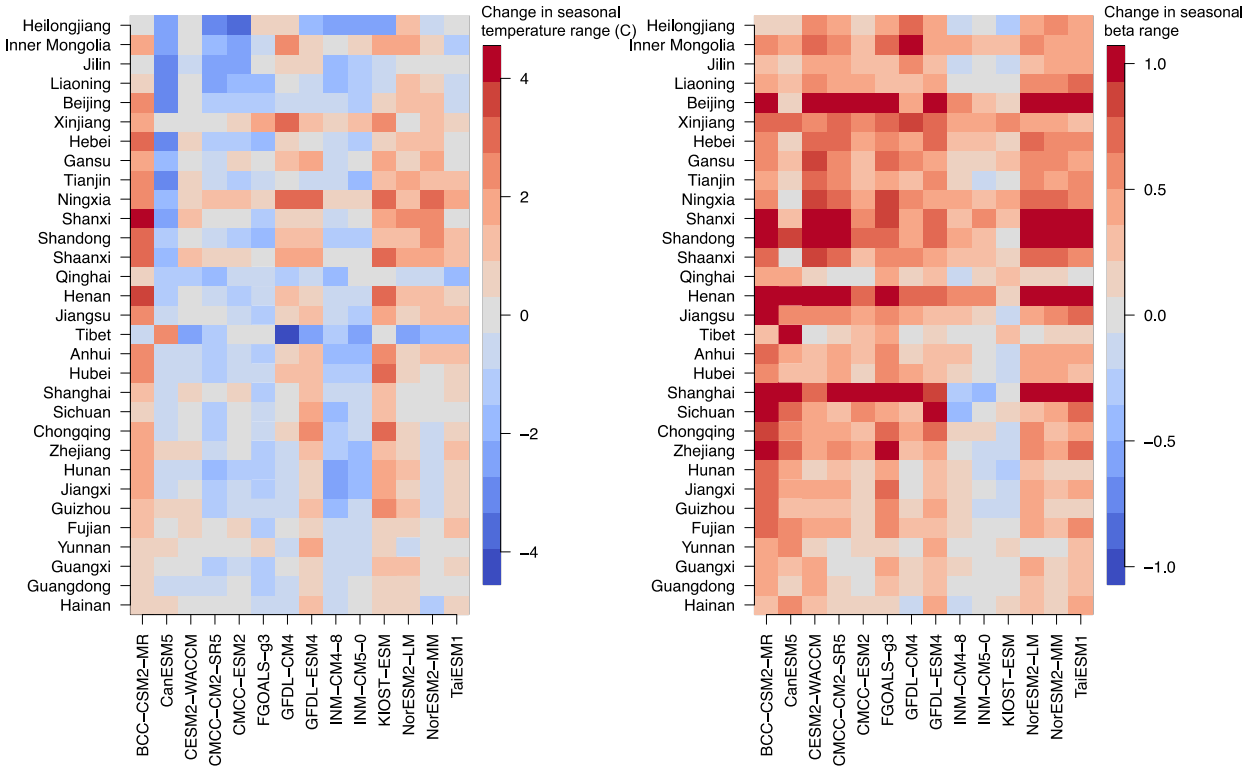
- For the climate projections, it feels like it should be mentioned that Hanan has consistent high peak size for CVA16, and why this is (already hot and humid?). From other analyses of people living in hot and humid places, what is the feasibility of mitigation?

We find a somewhat complex relationship between the projected change to the seasonal range of temperature, the projected change in the range of transmission and the change to projected incidence. There are many locations where we project a decrease in the seasonal range of temperature, but the seasonal range of transmission increases (see second figure below for CVA16, now added to the supplementary materials – we already had this figure for EVA71). This is due to the exponential relationship between temperature and transmission (see first figure below). In the example below, although temperature range declines with climate change, the range of transmission increases (very slightly). Across almost all models we find that Henan has a projected increase in transmission range which leads to larger peak size outbreaks projected in the future.

A better discussion of the projected patterns is now included in the main text “An additional source of heterogeneity across climate models comes from the non-linear effect of temperature on transmission (Supplementary Fig. 7). In some locations, although the seasonal range in temperature declines, the seasonal range of transmission may increase due to the estimated convex temperature-transmission curve. This effect dominates for climate models, and locations, where the projected decrease in temperature change is marginal.” The figures below are included in the supplementary material.



Nonlinear effects of temperature on transmission -- CVA16}. In some cases the projected temperature range may decline relative to the baseline climate (x-axis color bars) and yet the transmission range may increase or stay the same (y-axis color bars) due to the nonlinear relationship between temperature and transmission.



- Please include how the results obtained in Fig 4 are derived, ie. Precisely what is used from an anova, RSS?

We apologize for not being clear in the description. Yes, the RSS is used. We have now updated the text.

"We then perform an analysis of variance (ANOVA) to analyse the relative role of these three factors in determining the outbreak size by calculating their contribution to the regression sum of squares (RSS)."

Note: github site was not accessible to review.

I am able to review code, but not accessible (private repo).

We apologize – we have now made the repo public.

Reviewer #3 (Remarks to the Author):

In this study, authors assess how the intensity of enterovirus outbreaks may change with climate change. To do this, considering the examples of polio, EVA71 and CVA16, they first assess how the transmission rates of these viruses are affected by temperature and other variables such as school holidays, looking at US and Chinese data. They then plug in these associations into a dynamical model to predict how enterovirus outbreak dynamics might change with of climate

change, considering different climate models to explore uncertainty about climate change. They find that we might expect an important rise in enterovirus outbreak sizes with climate change.

We thank the reviewer for taking the time to review the paper and for providing the helpful feedback below.

Overall, I found that this is an interesting and well written paper. However, I have one major comment/source of concern. In their model, authors implicitly assume that immunity conferred by enterovirus infection is life-long. However, I don't think that this assumption is realistic for enteroviruses as reinfections are likely common at a young age. In this context, I wonder what the impact of the assumption of life-long immunity has on the results. In particular, I'm concerned that introducing a decay of protection following infection, may affect estimates of the impact of climate change on outbreak size. I would therefore like to see a sensitivity analyses exploring the sensitivity of their estimates and forecasts to assumptions about the duration of protection following infection.

We agree with the reviewer: sequential infections with different enterovirus serotypes is common. However, it is unclear whether this applies to specific serotypes. Data on EV-A71 neutralization titers (which are considered a correlate of protection) suggest that antibody titers remain high over time and as such the seroreversion rate is low: longitudinal serological data from Yang et al (2022) estimated that the probability of EV-A71 seroreversion was <10% at 11 years of age. Furthermore, SIRS models with waning immunity fit to time series case data on EV-A71, CV-A16, and other non-polio enterovirus serotypes from Japan suggest that the duration of protective immunity is long-lasting, on the order of multiple years to life-long (Pons-Salort 2018).

For the nonpolio enteroviruses (EVA71 and CVA16) examined in the manuscript (in China and Japan), we develop serotype specific models with the assumption that immunity is life-long. We explicitly do not fit our model to all-cause case data for HFMD as young children may experience repeat HFMD infections caused by different enterovirus serotypes. Our TSIR approach relies on the assumption of serotype-specific life-long immunity. In the TSIR, the susceptible time series is reconstructed by regressing birth rates on cases with the assumption that all individuals are infected. The regression coefficient gives the reporting rate and the regression residuals are deviations from mean proportion of individuals who are susceptible.

New text in methods "This approach assumes that infection with a specific enterovirus serotype is immunizing. Data on EV-A71 neutralization titers (which are considered a correlate of protection) suggest that antibody titers remain high over time and as such the seroreversion rate is low: longitudinal serological data from Yang et al (2022) \cite{yang2022seroepidemiology} estimated that the probability of EVA71 seroreversion was $<10\%$ at 11 years of age.

Furthermore, SIRS models with waning immunity fit to time series case data on EVA71, CVA16, and other non-polio enterovirus serotypes from Japan suggest that the duration of protective immunity is long-lasting, on the order of multiple years to life-long \cite{pons2018seasonality}."

Other comments:
Figure 1A : Center of gravity usually refers to a spatial concept. Here however, it seems this corresponds to a temporal one, something along the lines of average week of case occurrence. It's not a standard terminology in this kind of analysis, so please define the concept clearly (I am not sure it's completely adapted for a temporal concept – so consider a term that would be more intuitive in such context).

We thank the reviewer for pointing out that "center of gravity" is not an intuitive concept for an interdisciplinary audience. We now use "mean timing of cases" and fully describe the calculation in the methods section under a new heading. The calculation is based on the physics concept, as the reviewer notes, and uses circular statistics (weeks are converted to radians). The reason we use this approach is that it accounts for the fact that cases may be clustered around week 1 and week 52 of the year. If we used a non-circular measure, the mean timing of e.g. 1 case in week 1 and 1 case in week 52 would be week 26.5, but a circular measure allows this to be week 0.5. Given enterovirus outbreaks are in the summer, this is less of a concern, but the approach is robust to wintertime outbreaks.

New text " Mean timing of cases

We calculate the mean timing of cases by calculating the center of gravity using the "circular" package in R, following \cite{park2021epidemiological}. The center of gravity calculates the arithmetic weighted mean timing of the cases. The formula is given by:

\begin{equation}

COG = 52*atan2(\sum_1^{52} I_w*sin(w),\sum_1^{52} I_w*cos(w))/(2\pi)

\end{equation}

where w is the week of year (from 1 to 52) converted to units of radians by $w = week/52*2\pi$, and I_w is the mean cases in week w, averaged across all years for a particular location."

I'd put the same subtitles in Fig 1A and B-D-C.

Updated- thanks for the suggestion.

Fig 1 B, D. I'd use the same range of x- and y-axis so it's easier to compare the different panels.

Updated – we now use constant x-axis and y-axis apart from the timing of polio cases which is later than EVA71 and CVA16 so we keep this on a different scale.

What is the blue area in Fig 1B,D?

The blue area was supposed to show the x-axis range of the polio plots in the EVA71 and CVA16 plot. We have now removed this as they are replotted on the same x-axis.

Fig 2B: left hand side: indicate what is being plotted on y-axis.

Updated..

Line 125: "based on estimates of school semester in China and Japan". Aren't data available for school semesters in these locations? If not, how are these time periods "estimated"? I don't understand what authors do to address historical data on school holidays that are not available for polio. Can't assumptions be made about the likely timing of holidays in the US at the time? Couldn't authors assume holidays at the time were roughly similar to what they are now?

For China and Japan, we were not able to find data on school timing for the whole time period so we assume the timing of semesters matches the present-day timing (accessed 2022). For the US, we expect the timing of schooling may have been substantially different in the 1940s (Pedersen 2012). As opposed to estimating the effect of schooling, we include weekly dummy variables that remove any national-level seasonal drivers of transmission that are constant across time period.

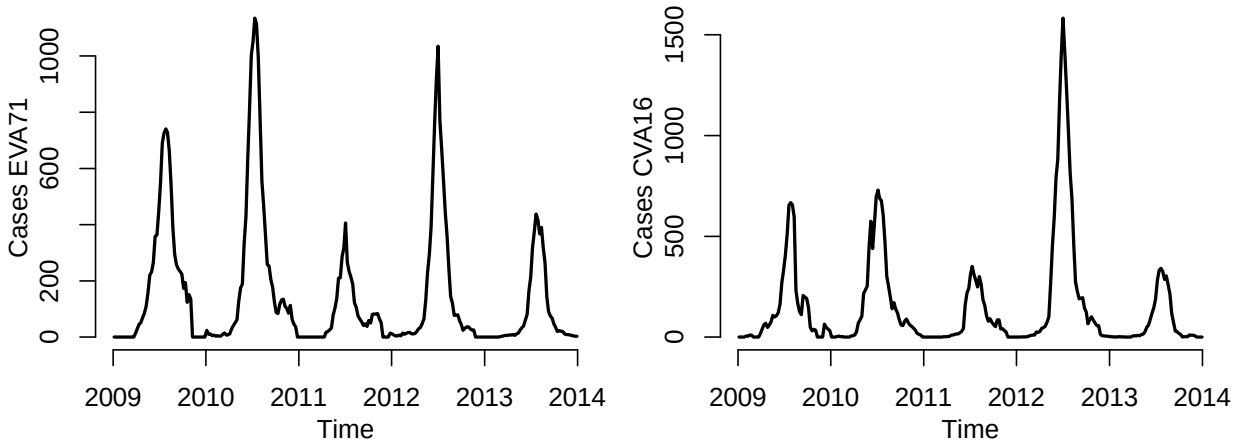
Line 145: "For locations with a large seasonal temperature range and higher mean transmission, our model predicts higher order outbreaks can occur". I don't think "higher order outbreak" will be clear for all readers. Please clarify.

We agree with the reviewer. New sentence "For locations with a large seasonal temperature range and higher mean transmission, our model predicts periodic, or even chaotic, outbreaks can occur. For instance, the model predicts that Liaoning in northern China may experience biennial outbreaks, defined as alternating years of high and low case numbers."

"For instance, the model predicts that Liaoning in northern China may experience biennial outbreaks, defined as alternating years of high and low case numbers. Our observational data suggests that biennial outbreaks occur in Liaoning; biennial outbreaks have also been observed in other enterovirus time series in other locations [14]." If that's the case, authors should show the data. Could be in Supplementary Material. The left hand side of Fig 2B shows seasonal

variations over a year; but right hand side panels predicts variations over sometimes multiple years. It would be nice if authors could show variations of cases over multiple years.

We agree with the reviewer. We now include the plot below in the supplementary material (Supplementary Fig. 4). Biennial outbreaks are observed for both serotypes – but more markedly for EVA71. This figure is referenced in the text.



New text: “Our observational data suggests that biennial outbreaks occur in Liaoning (Supplementary Fig. 4).”

In the graph, the model predicts that in some locations, outbreaks may occur only every 3 years. Are there locations consistent with such patterns.

Our China time series are too short to discern triennial outbreaks (or higher periodicities). However, in Japan time series there are periods of triennial outbreaks for both CVA16 and EVA71 (see the wavelet analysis conducted by Takahashi et al 2018 of this data). Our simulation results suggest that triennial dynamics are likely not very stable i.e. these occur in limited areas of Fig. 2B such that small changes in mean transmission may shift the predicted outbreak pattern. This may explain why triennial patterns are not observed consistently in the Japanese time series.

We also note that to generate Fig. 2B we must hold birth rates and population constant (otherwise we would need another axis to show how this surface evolves under different birth rates). The Japanese birth rate is sufficiently different from Chinese locations that we do not show Japan on this surface.

We note in the text “Triennial outbreaks have also been observed in transient in Japan \cite{takahashi2018epidemic}, and other locations \cite{pons2018seasonality, pons2018serotype}.”

Fig 2E: “The ratio of the schooling peak to temperature peak for locations with two annual peaks for EVA71” I don’t understand what these are and how they are computed. Label in y-axis in 2E: what is “mean transmission”? What are the definitions of schooling and temperature peaks?

When we fit the regression model we include a location specific fixed effect. This captures the fact that transmission may be higher or lower in specific locations due to factors such as population connectivity and density (for example Beijing has higher on average transmission than Tibet). Mean transmission in the plot is the sum of this location specific transmission value and the regression model intercept (which is constant across all locations). We have now changed “mean transmission” to “baseline transmission” as this more accurately reflects how this parameter is generated.

For the peaks, we calculate the average modeled cases with one year and use the find_peaks function in R (https://github.com/stas-g/findPeaks). This function defines a peak as a point such that “m” points either side of it has a lower or equal value to it where we set “m” to 3. In Fig 2B, periodcity = 0.5 is defined as all simulations where we identify two peaks. In Fig. 2E we calculate the ratio of the size of the second peak to the size of the first peak within a year. We assume the first peak is the “temperature” peak as this scales with increases in temperature range.

We thank the reviewer for pointing out the lack of clarity in the text over the methods for generating the simulations in Fig. 2B-E. We have now added a new section in the methods to explain how these figures were generated. See “Present-day simulations”.

Reference

Baker, Rachel E., et al. "Long-term benefits of nonpharmaceutical interventions for endemic infections are shaped by respiratory pathogen dynamics." *Proceedings of the National Academy of Sciences* 119.49 (2022): e2208895119.

Baker, Rachel E., et al. "Epidemic dynamics of respiratory syncytial virus in current and future climates." *Nature communications* 10.1 (2019): 1-8.

Deng, Huixiong, et al. "Development of a multivalent enterovirus subunit vaccine based on immunoinformatic design principles for the prevention of HFMD." *Vaccine* 38.20 (2020): 3671-3681.

Park, Sang Woo, et al. "Epidemiological dynamics of enterovirus D68 in the United States and implications for acute flaccid myelitis." *Science Translational Medicine* 13.584 (2021): eabd2400.

Pedersen, James. "The History of School and Summer Vacation." *Journal of Inquiry and Action in Education* 5.1 (2012): 54-62.

Pitzer, Virginia E., et al. "Environmental drivers of the spatiotemporal dynamics of respiratory syncytial virus in the United States." *PLoS pathogens* 11.1 (2015): e1004591.

Pitzer, Virginia E., et al. "Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics." *Science* 325.5938 (2009): 290-294

Pons-Salort, Margarita, et al. "The seasonality of nonpolio enteroviruses in the United States: Patterns and drivers." *Proceedings of the National Academy of Sciences* 115.12 (2018): 3078-3083.
Pons-Salort, Margarita, and Nicholas C. Grassly. "Serotype-specific immunity explains the incidence of diseases caused by human enteroviruses." *Science* 361.6404 (2018): 800-803.

Takahashi, Saki, et al. "Epidemic dynamics, interactions and predictability of enteroviruses associated with hand, foot and mouth disease in Japan." *Journal of the Royal Society Interface* 15.146 (2018): 20180507.

Yang, Juan, et al. "Seroepidemiology of enterovirus A71 infection in prospective cohort studies of children in southern China, 2013-2018." *Nature Communications* 13.1 (2022): 7280.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Comment 1

I want to follow-up on the response to my previous comment number 3, regarding the possible effect of relative humidity.

The authors have now tested the individual role of relative humidity and do not find a significant effect on transmission.

In their response, they point that dew point temperature was a better predictor than temperature in a previous study using data from the USA (Pons-Salort 2018). My guess is that the dew point temperature is better because it accounts for the effect of temperature modulated by changes in relative humidity, which are intrinsically linked to elevation. This relates to a comment from Reviewer 2 about some of the states being outliers in Baker's et al manuscript, e.g. Nevada and Tibet, which it turns out that are at high altitude.

I think the authors should test whether the dew point temperature is better than temperature at explaining transmission. (It should be possible to obtain dew point temperatures from measures of temperature and relative humidity).

Comment 2

I also want to comment on the authors' response to the main comment from Reviewer 3:

- To my knowledge, there is no scientific evidence that serotype-specific neutralising antibodies in blood are a correlate of protection against homotypic enterovirus infections (although they might be against symptomatic disease).
- Reinfections with the same serotype might happen – see e.g. Huang et al. Epidemiology of recurrent hand, foot and mouth disease, China, 2008-2015. EID (2020) DOI: 10.3201/eid2403.171303

The authors must correct their statements or alternatively, provide evidence of those.

Reviewer #2 (Remarks to the Author):

The authors have fully responded to my and others comments from reviewers. well done, the study is a nice addition to understanding climate change effects on pathogens.

Reviewer #2 (Remarks on code availability):

I haven't run the code, but the readme provides sufficient details. the code is available for all the results and plots.

Reviewer #3 (Remarks to the Author):

In general, I'm happy with authors' responses to my initial comments. But I would still like to see more discussion about the assumption that immunity is life-long and how results might be modified if this was not the case.

Reviewer #1 (Remarks to the Author):

Comment 1

I want to follow-up on the response to my previous comment number 3, regarding the possible effect of relative humidity.

The authors have now tested the individual role of relative humidity and do not find a significant effect on transmission.

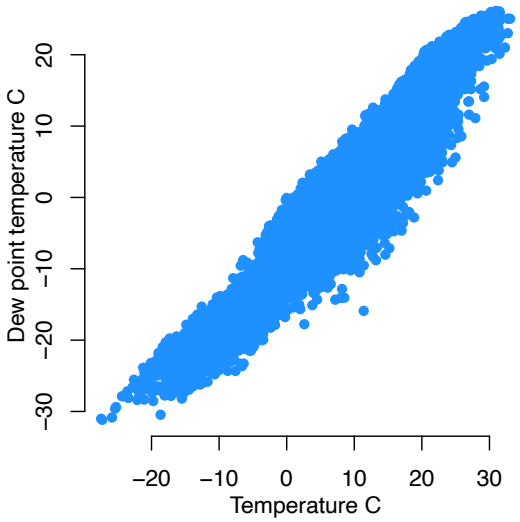
In their response, they point that dew point temperature was a better predictor than temperature in a previous study using data from the USA (Pons-Salort 2018). My guess is that the dew point temperature is better because it accounts for the effect of temperature modulated by changes in relative humidity, which are intrinsically linked to elevation. This relates to a comment from Reviewer 2 about some of the states being outliers in Baker's et al manuscript, e.g. Nevada and Tibet, which it turns out that are at high altitude.

I think the authors should test whether the dew point temperature is better than temperature at explaining transmission. (It should be possible to obtain dew point temperatures from measures of temperature and relative humidity).

We have now tested the effect of dewpoint temperature on transmission using dew point temperature data derived from ERA5. We find that the effect of dew point temperature on transmission is significant for both EVA71 and CVA16 however, this is expected given the strong correlation (and theoretical association) between temperature and dew point temperature (see figure below).

We find that dew point temperature is a marginally worse predictor of transmission than temperature. For EVA71 R^2 values of the regression of dewpoint temperature and temperature on transmission are 0.833 and 0.834 respectively and for CVA16, 0.534 and 0.537 respectively. P-values for the effect of temperature on transmission of EVA71 and CVA16 are marginally more significant than for dew point temperature (0.00158 T vs 0.00422 DPT, EVA71; 0.000987 T vs 0.00466 DPT CVA16). We have now included these results in the supplementary materials (Table 3).

We note that Pons-Salort also found very close results for dew point temperature and temperature. Given the high correlation between these variables it may be impossible to categorically determine which is the dominant driver. However, laboratory experiments may help improve understanding of the association between relative humidity, temperature and enterovirus transmission and could help inform future work in this area. We note that our climate change projections are unlikely to change in either case; given assumptions of constant relative humidity under climate change (Douville et al. 2022), changes will be driven by the temperature component of the dew point temperature calculation.



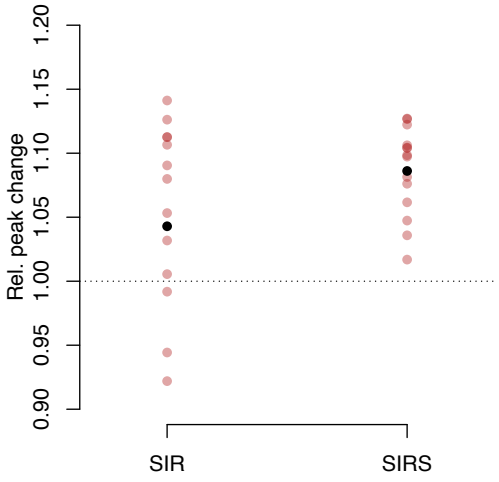
Comment 2

I also want to comment on the authors' response to the main comment from Reviewer 3:

- To my knowledge, there is no scientific evidence that serotype-specific neutralising antibodies in blood are a correlate of protection against homotypic enterovirus infections (although they might be against symptomatic disease).
- Reinfections with the same serotype might happen – see e.g. Huang et al. Epidemiology of recurrent hand, foot and mouth disease, China, 2008-2015. EID (2020) DOI: 10.3201/eid2403.171303

The authors must correct their statements or alternatively, provide evidence of those.

We thank the author for recommending Huang et al. 2020 – we found this was a very interesting study. Huang et al do find evidence of serotype-specific recurrence, however, the numbers are low (0.05% for EVA71 infections and 0.04% for CVA16). We have edited the methods text to reflect these findings (lines 350 – 353).



Edited text in methods “This approach assumes that infection with a specific enterovirus serotype is immunizing. Data on EV-A71 neutralization titers suggest that antibody titers remain high over time and as such the seroreversion rate is low: longitudinal serological data from Yang et al (2022) \cite{yang2022seroepidemiology} estimated that the probability of EVA71 seroreversion was $<10\%$ at 11 years of age. Furthermore, SIRS models with waning immunity fit to time series case data on EVA71, CVA16, and other non-polio enterovirus serotypes from Japan suggest that the duration of protective immunity is long-lasting, on the order of multiple years to life-long \cite{pons2018seasonality}. However, Huang et al. 2018 \cite{huang2018epidemiology} find small rates of recurrence of HFMD infection with the same serotype: 0.05\% for EVA71 and 0.04\% for CVA16. ”

We have also conducted a sensitivity analysis by developing projections using a SIRS model where we assume the rate of return to susceptibility based on the Huang et al estimates. The figure above shows the relative change in peak size (future projected peak size/ historic modeled peak size) for each CMIP6 model under the SIR model and SIRS model using climate for Beijing (note we assume the dependency of climate on transmission is the same for each model). We find that the projected mean change in peak size is slightly larger for the SIRS model than SIR model; however it does not substantially change our projection results (the mean change in peak size was not found to be significantly different across the SIR and SIRS model projections $p = 0.087$). This is because the SIRS model has slightly more stable dynamics than the SIR model (i.e. the SIRS dynamics are less likely to bifurcate than the SIR dynamics). We have now added this figure to the supplement and discussed this additional analysis in the methods section.

Reviewer #2 (Remarks to the Author):

The authors have fully responded to my and others comments from reviewers. well done, the study is a nice addition to understanding climate change effects on pathogens.

We thank the reviewer for their comments which have helped improve the manuscript!

Reviewer #2 (Remarks on code availability):

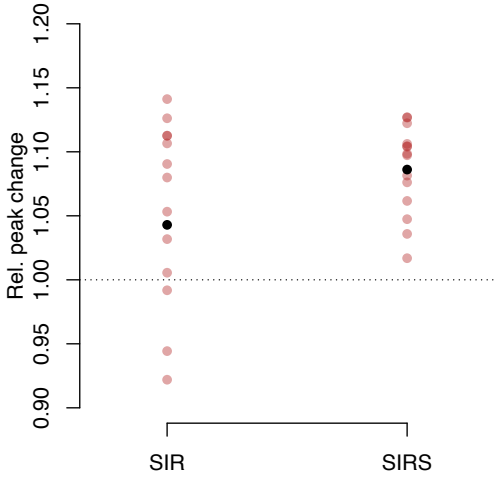
I haven't run the code, but the readme provides sufficient details. the code is available for all the results and plots.

Reviewer #3 (Remarks to the Author):

In general, I'm happy with authors' responses to my initial comments. But I would still like to see more discussion about the assumption that immunity is life-long and how results might be modified if this was not the case.

We have now conducted an additional sensitivity analysis to explore the implications for a SIRS model. This was conducted in response to comments from both Reviewer 1 and Reviewer 3. Text and figure repeated below for completeness:

We have also conducted a sensitivity analysis by developing projections using a SIRS model where we assume the rate of return to susceptibility based on the Huang et al estimates. The figure below shows the relative change in peak size (future projected peak size/ historic modeled peak size) for each CMIP6 model under the SIR model and SIRS model using climate for Beijing (note we assume the dependency of climate on transmission is the same for each model). We find that the projected mean change in peak size is slightly larger for the SIRS model than SIR model; however it does not substantially change our projection results (the mean change in peak size was not found to be significantly different across the SIR and SIRS model projections $p = 0.087$). This is because the SIRS model has slightly more stable dynamics than the SIR model (i.e. the SIRS dynamics are less likely to bifurcate than the SIR dynamics).



We have now added this figure to the supplement and discussed this additional analysis in methods section.

Reference

Douville, Hervé, et al. "Global warming at near-constant tropospheric relative humidity is supported by observations." *Communications Earth & Environment* 3.1 (2022): 237.