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2 Seasonal forecasting and health impact models: challenges and opportunities

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33

34 Abstract

35

36 After several decades of intensive research, the steady improvement in our ability to understand and
37 model the climate system has led to the release of the first generation of operational health early warning
38 systems in the so-called era of climate services. These schemes are based on multidisciplinary collaborations
39 across science disciplines, bringing together real-time climate and health data collection, state-of-the-art
40 seasonal climate predictions, epidemiological impact models based on historical data, and an understanding
41 of end-user and stakeholder needs. In the present review, we discuss the challenges and opportunities of this
42 kind of complex, multidisciplinary collaboration, with a particular focus on the factors limiting the role of
43 seasonal forecasting as a source of predictability for climate impact models.

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45

46 1. Introduction

47

48 The environmental consequences of climate change, such as sea-level rise, flooding and drought, more
49 intense hurricanes and storms, heat waves and degraded air quality, make substantial impacts on human well-
50 being¹. The health effects of these disruptions include population displacement, injury and death related to
51 extreme weather events, changes in the prevalence and geographical distribution of food-, water- and vector-
52 borne diseases, increased respiratory and cardiovascular disease and threats to mental health^{2,3}. Climate has a
53 potentially large impact on the incidence of vector-borne diseases, such as dengue and malaria⁴. This is felt
54 either directly, by affecting the developmental rates and survival of both the mosquito and pathogen, or
55 indirectly, through changes in land cover and land-surface characteristics, which affect the availability of
56 mosquito breeding sites^{5,6}. In addition, the climate interacts with local conditions and population herd
57 immunity, affecting not only mosquito infestation, but also human susceptibility and the contact rate between
58 mosquitoes and humans⁷.

59 As well as climate variability and change, infectious disease emergence and spread can be exacerbated

60 by anthropogenic activities, such as deforestation, mining, urbanization and human mobility⁸. For example,
61 the global expansion of the mosquito-transmitted viral disease, dengue fever, and the recent spread of
62 chikungunya and Zika viruses to the Americas, has been attributed, in part, to international travel and
63 ineffective vector control⁹. In Europe, the climate is becoming increasingly suitable for the mosquito species
64 *Ae. albopictus*, which is already established in several southern European countries. In 2010, locally acquired
65 dengue infections were reported in France and Croatia, and in 2012, an outbreak of more than 2000 dengue
66 cases occurred in Madeira, Portugal, in areas where *Ae. aegypti* exists¹⁰. Deforestation and mining activities in
67 the Amazon rainforest have coincided with an upsurge of malaria, due to the creation of natural and man-
68 made mosquito breeding sites and clustering of non-immune migrants close to these sites^{11,12}. For some
69 diseases, the most important factors may be the contact among people and wildlife that harbor zoonotic
70 pathogens¹³. For example, in tropical urban slum environments, epidemics of the bacterial disease
71 leptospirosis can occur during periods of heavy rainfall¹⁴. Flooding can lead to human infection after direct
72 contact with flood waters contaminated with the urine of infected rats. On the other hand, the transmission of
73 water and food-borne bacterial diseases, such as cholera or *E. coli*, is exacerbated by poor sanitation and
74 hygiene¹⁵.

75 Mitigation of climate change and adaptation to its negative effects are public health priorities in the
76 coming decades. The impacts of climate on health are felt across all sectors of society, from the local to the
77 global level, and climate change is becoming a central issue in public health and global political agendas¹⁶.
78 Infectious disease epidemics and extreme temperature-related mortality have a direct impact on the health of
79 local populations, strain healthcare systems, and cause substantial economic loss^{17,18}. Policy-makers are aware
80 of the effects of climate on the dynamics of many diseases and health outcomes. However, despite this
81 understanding, climate information is rarely exploited as a means to help prevent and control such health
82 risks¹⁹. To improve the ability to adapt to a changing climate and mitigate its effects, it is necessary to improve
83 the linkages between the production and supply of climate-science information and its accommodation to end-
84 users needs. Climate services, which aim to provide timely, tailored information and decision-support tools to
85 decision makers, are an important part of improving our capacity to manage climate-related risk²⁰. The Global

86 Framework for Climate Services (GFCS) is a climate service coordinating body, created in 2012 and led by the
87 World Meteorological Organization²¹. The GFCS aims to create a structure to support better, more informed
88 decisions, with the ultimate goal of saving lives, protecting the environment, and improving economic
89 development. The GFCS has so far focused efforts on developing countries, with health selected as one of its
90 priority sectors.

91 In this article, we discuss the challenges associated with incorporating climate information in health
92 impact models to understand variations in health risks. We first discuss spatio-temporal modeling tools of
93 climate impacts and diseases, and then we outline some the factors limiting the role of seasonal forecasting as
94 a source of predictability for these climate impact models, such as the transfer of predictable information, the
95 transient nature of climate teleconnections or the time-varying relationship between climate and associated
96 impacts.

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99 2. Spatio-temporal modeling of climate impacts and diseases

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102 Infectious diseases can be modeled by spatio-temporal statistical methods²². These tools, which tend to
103 be of an empirical kind rather than rooted in scientific mechanisms, are widely used in both environmental
104 and health sciences applications. In considering the many possible statistical models for disease processes, the
105 distinction between empirical and mechanistic models is important. An empirical model seeks only to describe
106 the spatio-temporal structure of the process, whereas a mechanistic model seeks to explain it. For example, an
107 empirical model might represent the behavior of the disease process by specifying the mean value at every
108 time and location as a regression on one or more spatially and/or temporally varying covariates, and the
109 covariance between any two values as a function of their spatio-temporal distance; whereas a mechanistic
110 model would more likely incorporate an explicit and asymmetric dependence between the present and the
111 past, for example by specifying disease risk at any particular time and location, conditional on the historical

112 incidence pattern.

113 The distinction between empirical and mechanistic modeling is sometimes equated to the distinction
114 between mathematical and statistical modeling, respectively. But this is at best an over-simplification. Data
115 relating to the scientific process of interest are invariably noisy. For this reason, whichever approach is taken
116 to modeling the scientific process, it is necessary to supplement the process model by a data model, which
117 specifies the joint distribution of the data conditional on the underlying temporal sequence of spatial states of
118 the process, and this model is inherently statistical. In practice, this hierarchical structure, combining a process
119 model with a data model conditional on the unobserved state of the process, is particularly important when
120 analyzing data with a relatively low signal-to-noise ratio. The data model is typically of limited scientific
121 interest in itself, but is essential to the delivery of valid inferences about the underlying process.

122 Empirical spatio-temporal models typically take the form of generalized linear models in which either
123 the regression parameters or the residuals are replaced by stochastic processes. In particular, Bayesian
124 geostatistical approaches, which replace the residual by a spatially and/or temporally correlated stochastic
125 process, are increasingly used for mapping the incidence of both infectious and non-infectious diseases²³.
126 These methods can be used for the identification of important covariates along with estimation of their
127 regression parameters, and for the prediction and mapping of future, unobserved values of the response
128 variable of interest. Also, they can provide valuable information for improving the design of future studies by
129 identifying and quantifying sources of variation that could be better controlled, or even eliminated altogether.

130 In contrast, mechanistic models typically use deterministic or stochastic differential equations to express
131 the dynamics of an underlying infectious disease process. Early accounts of this approach include a pair of
132 articles by Refs. 24-25. A more recent book-length account is Ref. 26. When locations and times of individual
133 cases are available, mechanistic models can be formulated as spatio-temporal point processes in which the
134 current incidence depends explicitly on the locations and times of past cases. Ref. 27 used this approach to
135 model the spread of the 2001 foot-and-mouth epidemic in the United Kingdom. The ability to combine
136 mechanistic models with principled, i.e. likelihood-based, methods of statistical inference is relatively recent.
137 It has been shown how a partial likelihood method due to Ref. 28 could be used to fit the Ref. 27 model. Ref.

138 29 showed that widely used empirical models of spatial correlation can be derived as the solutions to particular
139 kinds of stochastic differential equations, thereby rendering these models amenable to likelihood-based
140 inference.

141 A versatile modeling procedure was recently developed to determine the most important drivers of
142 spatio-temporal variability in disease risk³⁰. The model framework combines climatic and non-climatic factors
143 in the model parameterization to correctly quantify variability captured by climate information. The
144 methodology exploits recent advances in spatio-temporal hierarchical mixed modeling. An advantage of
145 implementing the model in a Bayesian framework is the ability to address specific public health issues in terms
146 of probabilities. Explanatory variables at various spatial and temporal resolutions (e.g. data on climate, land-
147 use, socio-economic conditions, health infrastructure, etc) can be incorporated and tested in the model
148 framework, to select a suitable combination of statistically significant variables. However, when health
149 outcome and climate data are both available, they are not necessarily measured at the same set of spatio-
150 temporal points, therefore a scale mismatch often exists. More generally, either or both of the health outcome
151 and climate data may take the form of spatial averages rather than point-referenced measurements. For
152 example, a common scenario is that health outcomes are recorded as case-counts and population
153 denominators on a set of small-area units that partition the region of interest, while ground truth
154 meteorological data are collected as time series at each location in an irregular network of weather-recording
155 stations. These data typically suffer from either or both measurement error and micro-scale fluctuations that
156 distort the underlying correct value. Data that are both spatially incomplete and error-prone are not necessarily
157 more useful than proxies such as remotely sensed images or the outputs from physically based climate models,
158 which are usually calculated on a raster grid³¹.

159 In principle, an extension of the hierarchical approach described above can accommodate multiple
160 spatially mis-aligned data sources by combining a spatially and temporally continuous process model with a
161 collection of spatially and temporally discrete data models, one for each data-source³². More pragmatically,
162 gridded data (e.g. climate or topographical) can be reconciled with spatial area data (e.g. disease counts and
163 demographic characteristics) using interpolation methods³³, or by assigning a grid point to each spatial

164 polygon on the basis of the shortest Euclidean distance between the area centroid and neighboring grid
165 points³⁴. Once all available explanatory data has been transformed to the same spatial and temporal resolution
166 as the response variable, it can be incorporated into the model framework to account for confounding factors
167 and help more correctly attribute variations in disease risk to variation in climatic factors.

168 In many cases, data on important drivers of disease systems are not routinely collected or readily
169 available. This limitation typically detracts from adequate progress in developing useful prediction systems
170 at the local scale of cities or small regions. To overcome this problem, spatio-temporal random effects can be
171 included in the model framework. Unstructured random effects help account for unknown or unobserved
172 disease risk factors (e.g. mosquito abundance, population immunity, health care inequalities and
173 interventions). Such effects introduce an extra source of variability (a latent effect) into the model, which can
174 assist in modeling overdispersion. To allow for correlated heterogeneity between locations or spatial
175 clustering, which is a typical feature of infectious disease dynamics, structured random effects can be included
176 in the model. One way to impose a spatial dependency structure is to assume a Gaussian intrinsic conditional
177 autoregressive model prior distribution for the spatial effects³⁵, which accounts for spatial dependence by
178 specifying a neighborhood structure of the area under consideration. Once unknown structures are accounted
179 for, we can identify which of the available indicators could significantly contribute to an effective early
180 warning system.

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183 3. Factors limiting seasonal forecasting as a source of predictability for climate impact models

184

185 Seasonal forecasts of the climate with lead times up to several months³⁶⁻³⁸, along with strong public
186 health surveillance systems, provide the opportunity to issue timely early warnings of imminent threats^{39,40}.
187 Several studies have investigated the use of climate information in early warning systems for diseases such as
188 malaria and Rift Valley fever^{41,42}. The efficacy of any climate-driven early warning system however strongly
189 depends on the underlying skill of the climate forecasting system. Seasonal climate forecasts have been

190 reported to have skill in tropical regions of Brazil and, to a lesser extent, in extratropical regions^{43,44}. For
191 example, in a recent study, real-time seasonal climate forecasts and disease surveillance data were integrated
192 into a spatio-temporal model framework⁴⁵, to provide a dengue forecast for Brazil, three months in advance
193 of a major global event (the 2014 FIFA World Cup⁴⁶). The probability of dengue incidence falling into pre-
194 defined categories of low, medium and high risk was mapped using a visualization technique in which color
195 saturation expresses forecast certainty⁴⁷. As an indication of the trust a decision maker can place in the dengue
196 predictions for a specific location, the forecast map was accompanied by a verification map, expressing the
197 past-performance of the model (see Figure 1). This climate-driven dengue early warning was used to support
198 the decisions of the National Dengue Control Programme several months ahead of the event, to help direct
199 mitigation and control actions to those areas with a higher probability of dengue outbreaks. The early
200 warnings were also disseminated to the general public via the media and visitors traveling to Brazil⁴⁸.

201 This example of successful early warning system illustrates the potential of climate services in terms of
202 health benefits. Nonetheless, there are several theoretical and practical issues to be considered that largely
203 limit the operational value of some of these schemes. These factors mainly refer to the scale-mismatch and the
204 transfer of predictable information from climate forecasts to the above-described models of climate-driven
205 impacts and diseases, which we proceed to discuss in the following subsections.

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207

208 3.1. Sources of climate predictability and transfer of predictable information

209

210 Although weather phenomena are not predictable at lead times beyond two weeks (i.e. the atmosphere
211 is chaotic⁴⁹), average values of climate variables are potentially predictable months, years and even decades in
212 advance⁵⁰. Nevertheless, the longer the lead time of the prediction, the longer the period of time for which the
213 variable needs to be averaged. The tropical belt plays a key role in the predictability of climate variables⁵¹,
214 which has an influence worldwide through the activation of atmospheric responses when thermally-driven
215 processes exceed certain thresholds. This region is largely influenced by the incident solar radiation that heats

216 the ocean surface, which in turn drives the atmospheric circulation, both locally and at distant regions through
217 large-scale teleconnections^{52,53}. Ocean anomalies, and thus these thermally-driven atmospheric patterns,
218 persist over longer periods than weather phenomena. Therefore, atmospheric variables are to some extent
219 predictable at lead times of months, years and decades⁵⁴. Climate forecasts at seasonal time-scales provide an
220 opportunity to anticipate potential health threats several months in advance. These forecasts occupy an
221 intermediate zone between weather forecasting and long-term climate projections, and are typically used to
222 issue probabilistic statements of the expected climate conditions for the next one to six months⁵⁴. These
223 forecasts are particularly skilful for certain seasons and locations around the world.

224 For example, El Niño-Southern Oscillation (ENSO) is a predictable phenomenon^{55,56} that is key to
225 seasonal climate forecasting worldwide^{57,58}. ENSO is a coupled oceanic-atmospheric phenomenon,
226 characterized by sustained fluctuations between unusually warm (El Niño) and cold (La Niña) sea surface
227 temperature conditions in the central and eastern tropical Pacific Ocean^{59,60}. ENSO influences the inter-annual
228 variability in weather patterns and the likelihood of activation, enhancement, weakening and/or displacement
229 of regional extreme events, such as droughts and floods, across the globe⁶¹⁻⁶³. Figures 2a,b exemplify the
230 associations that can be found between ENSO events and climate variables at distant regions several months
231 later. A negative relationship between Pacific sea surface temperatures in December-February and
232 precipitation the following March-May is observed for North Brazil, South East Africa and South East Asia,
233 implying dry conditions during El Niño events and wet conditions during La Niña events (Figure 2a). At the
234 same time of year, El Niño conditions are associated with anomalous warming over much of the Amazon,
235 South East Africa and Asia and North Australia (Figure 2b). An association between ENSO and a heightened
236 risk of certain vector-borne^{64,65}, water-borne^{66,67} and wind-borne^{51,68,69} diseases has been identified in specific
237 geographical areas where climate anomalies and ENSO are linked.

238 The potential predictability of climate variables in the tropics, and particularly that derived from ENSO,
239 is therefore key for the development of modeling tools to predict climate impacts and design early warning
240 systems^{41,46,70}. Nonetheless, there are other sources of predictability that can be explored for the use of climate
241 services⁷¹, and particularly in the mid-latitudes, where weaker atmospheric flow instabilities in summer favor

242 the influence of long memory drivers such as soil moisture⁷². Thus, the amount of available soil moisture
243 controls the fraction of heat that is released as latent and sensible heat fluxes, so that the frequency and
244 intensity of summer heat waves is largely controlled by the rainfall in the preceding winter and spring^{73,74}.
245 Some authors have however highlighted the complexity of this delayed association, and despite recent
246 advances in the prediction of heat waves, such as the record-breaking 2003 summer event in Europe⁷⁵, the skill
247 of these predictions remains rather poor. Ref. 76 for example showed that rainy winter/spring seasons over
248 southern Europe inhibit hot summer days whereas dry seasons are followed by either a high or a low
249 frequency of hot days. Ref. 77 later showed that summer heat is more sensitive to the occurrence of specific
250 weather regimes in initially dry cases than wet cases, inducing an asymmetry in summer heat predictability.

251 The still poor predictability of these forecasts represents a serious constraint for the applicability of
252 seasonal forecasts in the domain of climate services. For example, within the EUPORIAS project⁷⁸, a climate
253 service tool was developed to provide probabilistic predictions of exceeding emergency mortality thresholds
254 for heat wave scenarios⁷⁹. The predictions were based on sub-seasonal to seasonal temperature forecasts, to
255 support decision making for the preparedness of health services and protection of vulnerable communities
256 ahead of future extreme temperature events⁷⁹⁻⁸¹. The tool was designed to provide multi-lead probabilistic
257 forecasts of mortality risk ahead of the peak summer season. In general, a decreasing transition in skill was
258 found between excellent predictions when using observed temperature or weather forecasts at very short lead
259 times as driving climate conditions for the temperature-related mortality model, to predictions with no skill
260 when using forecast temperature with lead times greater than one week (Figure 3). This result showed that
261 the performance of climate services is in some cases more limited by the predictability of the climate variables,
262 and not by the impact model itself.

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265 3.2. The transient nature of climate variability and teleconnections

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267 Although a clear window of opportunity for climate services emerges during El Niño and La Niña years

268 in those areas with both climate predictability and large climate-driven disease incidence, there are several
269 factors limiting the potential use of this information in climate services. For example, predictability is generally
270 larger for surface air temperature than for precipitation, and therefore, the areas with large potential
271 predictability coincident in both variables are rather small. More importantly, ENSO should be seen as a non-
272 stationary mode of variability whose potential predictability and teleconnections change at the decadal and
273 longer timescales. Figures 2c-f illustrate the time-varying relationship between ENSO and climate variables
274 for two consecutive 30-year time periods, showing the transient nature of ENSO dynamics and
275 teleconnections. While there are large areas in the tropics with significant correlations with temperature in
276 both periods (cf. Figures 2d,f), we see no overlapping regions in the precipitation maps (cf. Figures 2c,e). We
277 find for example that a multidecadal regime shift in the late seventies decreased the relationship between
278 ENSO and the Asian monsoons⁸² (cf. Figures 2d,f), or that global warming is expected to favor the relative
279 occurrence of central Pacific El Niño events (also referred to as El Niño Modoki⁸³) to the detriment of the
280 canonical type in the eastern Pacific^{84,85}. These changes modify the areas and time lags that characterize the
281 associated teleconnections, whose non-stationary nature imposes a strong constraint to the calibration and
282 application of climate-driven impact models, being sensitive to regime shifts in the ENSO phenomenon, and
283 in general, in the climate system.

284 ENSO also exemplifies the intermittent relationship between climate and associated impacts at the
285 interannual timescale, for which El Niño and La Niña define transient windows of opportunity for enhanced
286 predictability. Despite the active search for climatic drivers of infectious diseases, the irregularity of this link
287 and the temporal scales of these windows impose a limit in our ability to anticipate disease risk, which
288 typically leads to low reported correlations between disease descriptors and climatic variables. Different
289 factors could explain these low values, ranging from climatic variables being inherently weak drivers of the
290 dynamics of the disease, or being strong modulators operating in a nonlinear way. The former can take place
291 when the forcing occurs only during limited intervals of time (for example, during El Niño or La Niña
292 episodes), or when local variation in environmental factors and the immunological status of the at-risk
293 population mask the underlying climate-related dynamics⁸⁶. The latter implies an association between

294 variables that is not fully addressed by standard statistical techniques, and can therefore be incorrectly
295 interpreted as a weak dynamical association. It is critical to distinguish between these different outcomes,
296 given that the information provided on the underlying processes is radically different. A strong coupling
297 between climate and disease variables, albeit transient in time or imperfectly measured, can provide potential
298 for long-lead disease forecasting.

299 A clear example was provided by the study of population dynamics of cholera epidemics in
300 Bangladesh⁶⁶, which demonstrated an influence of the ENSO phenomenon on the disease. However, this study
301 could not address the strength of this influence, given that the effect of the different independent variables
302 was not additive in the model, and changed over time. The clear relationship between temperature and the
303 amplification of cholera incidence worldwide has since been well documented^{67,87,88}. Nevertheless, there seems
304 to be an apparent discrepancy between known aspects of cholera epidemiology and the low values obtained
305 in correlations reported by many studies. This can be also seen, for example, in the relationship that was found
306 between cholera and rainfall in Zanzibar, where attained significance levels were low despite the known
307 strong relationships between extreme rainfall and the disease⁸⁹.

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310 3.3. The time-varying association between climate variability and impacts

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312 In addition to the transient nature of climate variability and associated teleconnections, temporal
313 changes in the association between climate metrics and impacts on health can also affect the applicability of
314 climate forecast information into impact models. Apart from secular changes in infrastructure and public
315 health, anthropogenic global warming due to human activities can also redefine these associations, whose
316 future evolution is not easy to anticipate because either the relationships are not fully understood or changes
317 in the key driving climate variables are still uncertain^{51,68}. In addition, the future evolution of the incidence of
318 certain diseases is closely determined by the degree of exposure of human individuals and societies, which
319 can change through a natural response of the body metabolism⁹⁰, the adoption of new habits by individuals

320 and populations⁹¹, or the design of societal strategies and measures aimed at reducing the vulnerability of their
321 citizens^{92,93}.

322 We here illustrate these points with regard to temperature-related mortality, whose expected increase
323 in summer probably represents the most direct consequence of temperature rise to human health^{18,94}. Recent
324 heat waves suggest that changes in the degree of exposure of human populations is not only the result of a
325 slow and progressive process due to background temperatures, but also a relatively rapid response to large
326 impact events. For example, Ref. 92 used a model that successfully predicted the death toll associated with the
327 record-breaking summer 2003 heat wave in France, and showed that the impact of heat waves changed after
328 the event: excess mortality predictions for the following heat wave in 2006 (6452 deaths) were found to largely
329 exceed the observed mortality (2065 cases). The study concluded that the overestimation in the prediction was
330 due to the decline of the vulnerability to heat, the increase in the awareness of the risk, the adoption of
331 preventive measures and the implementation of a coordinated early warning system.

332 This result suggests that the relation between climate variables and human mortality is constantly being
333 redefined, and therefore climate impact models need to be recalibrated accordingly⁹⁵. For example, Ref. 96
334 used spatiotemporal climate and mortality data in France to describe the dependency between long-term
335 changes in heat stress factors and their relationship with mortality. This study showed that the +1.2°C warming
336 in mean temperatures observed in recent decades was associated with a +0.7°C warming in the comfort
337 temperature (i.e. temperature of minimum mortality), suggesting that human populations have experienced
338 a set of long-term acclimatization mechanisms to slow-varying background temperatures. The response ratio
339 $0.7 / 1.2 \approx 0.58$ is found to be lower than 1, suggesting that this set of slow-varying acclimatization processes
340 might be partially limited by other factors, e.g. mechanisms linked to the physiology of the human body and/or
341 the natural dynamics of the pathogens associated with the seasonal rise of mortality in winter⁹⁷.

342 In this regard, Ref. 5 proposed a qualitative conceptual model in which the degree of exposure of a
343 society to summer temperatures is reduced under warming conditions (Figure 4a), and Ref. 80 later
344 hypothesized a scenario in which the rise in winter temperatures increases the sensitivity of individuals to
345 cold events (Figure 4b). These scenarios of exposure to warm and/or cold temperatures were used to infer

346 long-term projections of future annual mortality in Europe⁸⁰, showing that the rise in heat-related mortality
347 will start to completely compensate the reduction of deaths from cold during the second half of the century (R
348 $= 0$ in Figures 4c,d). Nevertheless, changes in annual mortality are seen to be small compared to those that are
349 inferred from scenarios of immediate gain or loss of acclimatization to warmer summer or winter
350 temperatures, respectively ($R = 1$ in Figures 4c,d). This result thus highlights the key importance of
351 uncertainties associated with the relationship between climate variability and impacts for the study of some
352 health effects.

353

354

355 4. Conclusions and future work

356

357 The health sector is starting to benefit from tailored climate services based on climate forecasts, to
358 support decision making at local, regional, national and global levels. Health stakeholders include government
359 ministries and departments, hospitals and other health services⁹⁸. These agencies are starting to make use of
360 climate impact indicators to optimize the resources in the health system, and to enforce preventive measures
361 to improve quality of life, particularly for the most vulnerable sectors of society. However, information from
362 climate forecasts used in operational early warning systems requires a rigorous assessment of its real
363 predictability and applicability. Moreover, factors determining the vulnerability to adverse health effects,
364 including biological susceptibility, socio-economic status and the built environment, also need to be
365 considered in the decision making process. Only in this way, by integrating useful climate and non-climate
366 information in decision-support systems, policy makers are expected to be best placed to mitigate and adapt
367 to the environmental effects of climate change in the most efficient ways possible. Despite some progress in
368 demonstrating the potential for incorporating climate information into public health decision-making
369 processes, there remain substantial challenges to the implementation of sustainable operational early warning
370 systems. They require significant financial resources and long-lasting inter-agency collaboration to stand a
371 chance of being successful. Further, effective communication of tailored climate information⁹⁹, an iterative

372 evaluation of the efficacy of the system²⁰ and local capacity building are necessary components to achieve
373 effective and sustainable services.

374 The many potential drivers of complex health systems, both extrinsic (e.g. climate and socio-economic
375 factors) and intrinsic (e.g. population immunity, vulnerability and demography) are often difficult to
376 disentangle. Spatio-temporal modeling tools are therefore required to simultaneously consider the complex
377 interaction of climate hazards, disease transmission, socio-economic disparities and human vulnerability in
378 predictive health risk models. There is however an urgent need for more interdisciplinary collaboration to
379 make available global datasets of important health risk factors, and to understand the caveats associated to
380 each dataset before embarking on modeling exercises. New endeavors are required to synthesize data
381 collection and modeling efforts, and to design health early warning systems in close collaboration with public
382 health decision makers.

383 These initiatives also depend on the availability of accurate climate information and skilful climate
384 forecasts for the implementation of operational early warning systems. There are windows of opportunity for
385 the prediction of climate variables with lead-times from months to a few seasons, especially during El Niño
386 and La Niña episodes and in ENSO affected regions. Climate forecasts are found to be more accurate during
387 these events, particularly in the tropics where climate-sensitive diseases pose the largest burden to public
388 health. When these events occur, there is a clear opportunity to incorporate climate information into decision-
389 making processes for climate-sensitive sectors, also out of the tropics due to the nature of atmospheric
390 teleconnections. Nonetheless, this information is subject to large uncertainties associated for example with the
391 complex and non-stationary nature of the climate system. Moreover, the skill of the climate forecasts rapidly
392 decreases when these windows of opportunity close, which in many cases can make the information provided
393 in the climate service systems no better than a coin toss. In that regard, the skill of climate model simulations
394 and predictions still represents a major research area for improving the usefulness of health early warning
395 systems to public health decision-makers, particularly in those many regions and time-scales for which climate
396 forecast skill is low or non-existent.

397 In conclusion, future endeavors aimed at developing new scientific tools and platforms for the

398 mitigation of climate-related health risks and the adaptation of society to environmental emergencies will
399 require the close coordination of climate modelers and scientists, epidemiologists, hospitals, public health
400 agencies and governments. This will help ensure the successful implementation and delivery of useful tools
401 for the well-being and adaptation of society to the threats posed by climate change.

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418 Conflicts of interest

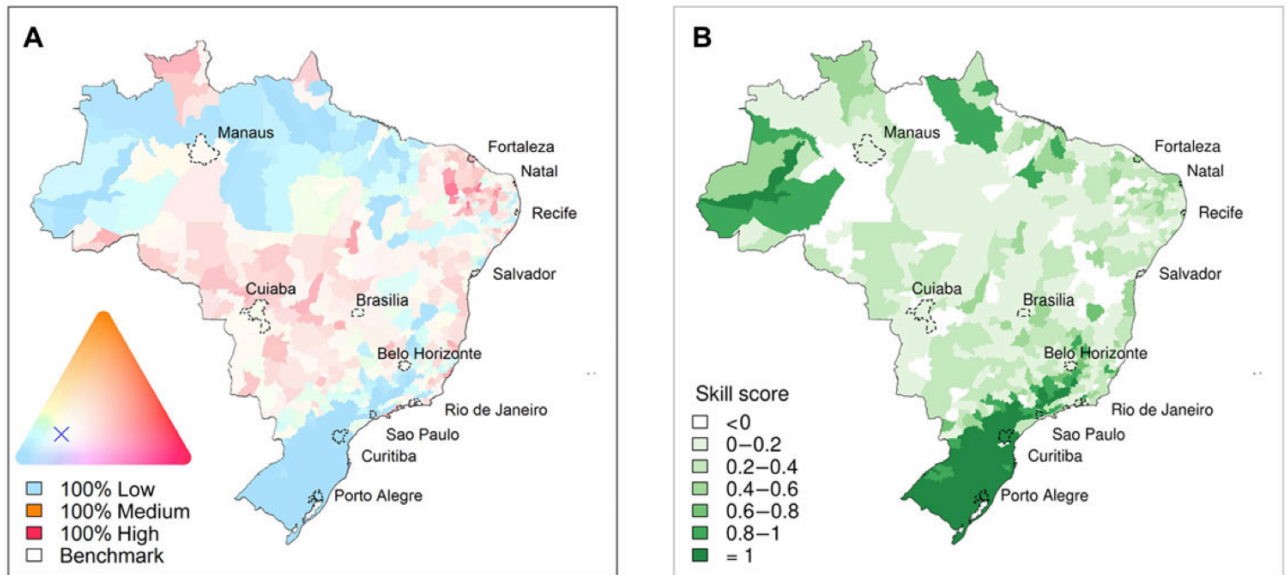
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420 The authors declare no conflicts of interest.

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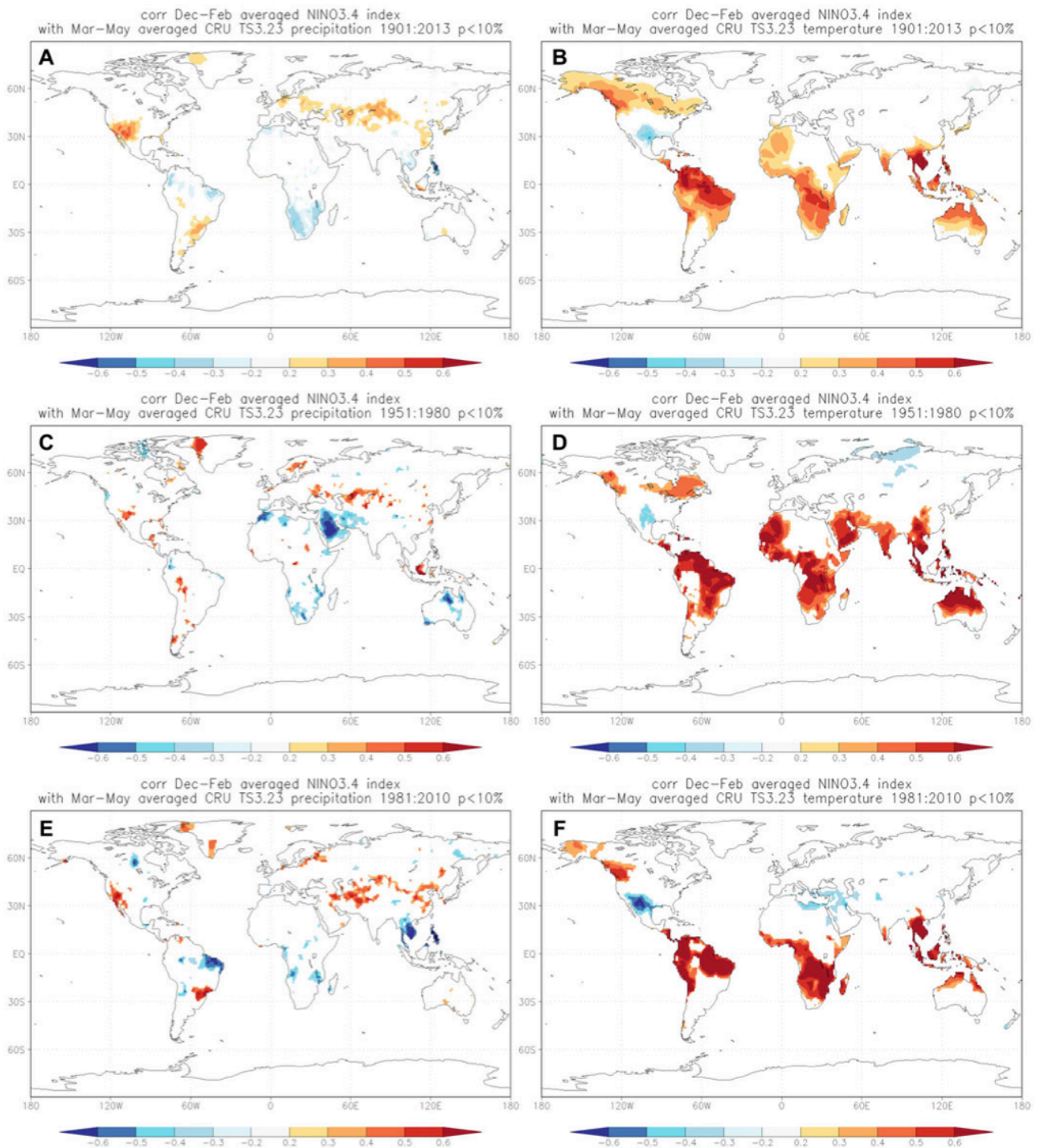
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Figure 1. (a) Probabilistic dengue forecast for Brazil, June 2014. The continuous color palette (ternary phase diagram) conveys the probabilities assigned to low-risk, medium-risk and high-risk dengue categories. Category boundaries are defined as 100 cases per 100,000 inhabitants and 300 cases per 100,000 inhabitants. The greater the color saturation, the more certain is the forecast of a particular outcome. Strong red shows a high probability of high dengue risk. Strong blue indicates a high probability of low dengue risk. Colors close to white indicate a forecast similar to the benchmark, i.e. long-term average distribution of dengue incidence in Brazil, marked by a cross. (b) Evaluation of past performance for each area based on out-of-sample retrospective dengue forecasts, June 2000-13. The skill score takes the value one for a perfect forecast and zero for the benchmark (long-term average) forecast. The darker the shade of green, the greater the skill of the forecasting system. Negative values (white) show areas where the model did worse than using the benchmark. Adapted from Ref. 46.



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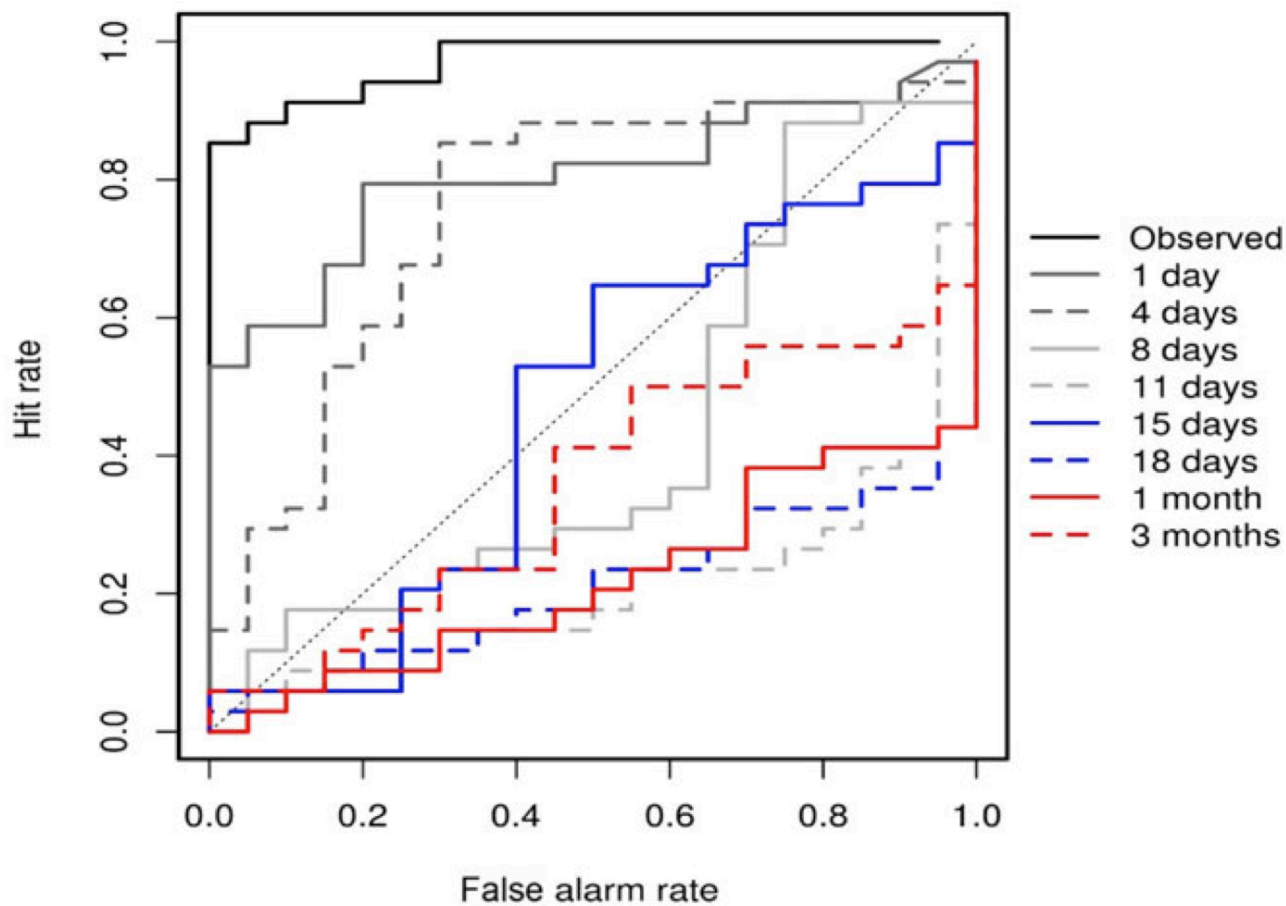
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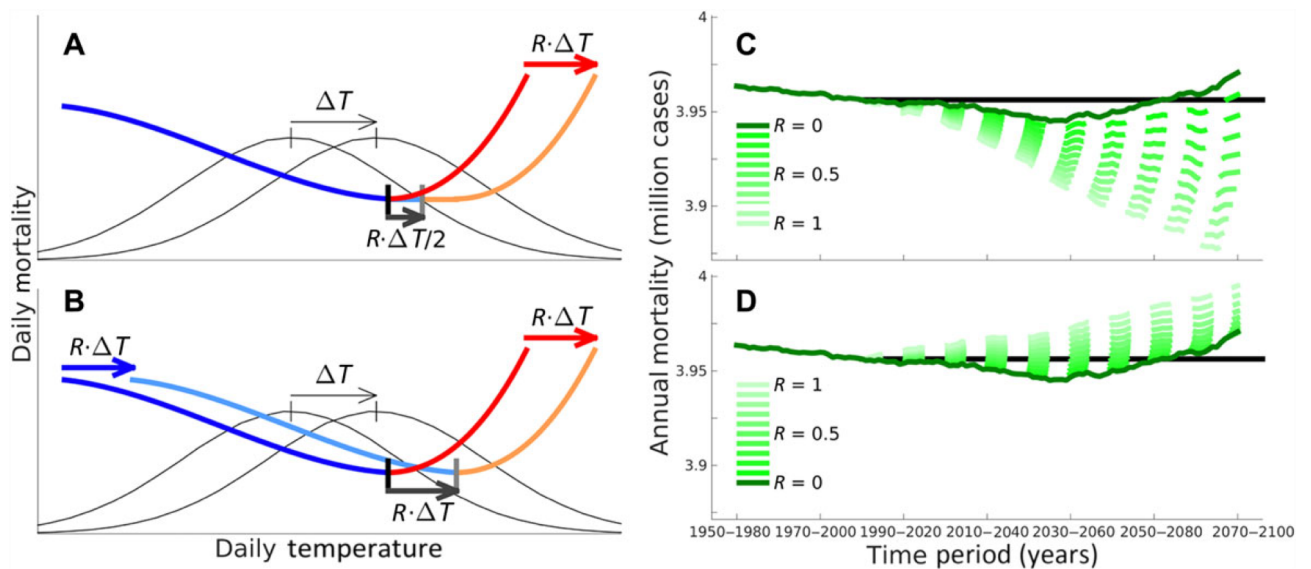
Figure 2. Maps of statistically significant (at the 10% level) correlations between December-February sea surface temperature anomalies in the Nino3.4 region (170-120W, 5S-5N) and March-May global precipitation (a,c,e) and temperature (b,d,f). Data is taken from the Climatic Research Unit dataset for 1901-2013 (a,b), 1951-1980 (c,d) and 1981-2010 (e,f), and maps are produced using KNMI Climate Explorer (<http://climexp.knmi.nl>).



442

443 Figure 3. Receiver Operating Characteristic (ROC) curves for the binary event of exceeding an
 444 emergency mortality threshold in Europe for a heat wave scenario (1-15 August 2003), using a probabilistic
 445 mortality model driven by climate forecast data at lead times ranging from 1 day to 3 months. The ROC curve
 446 for the mortality model driven by observed climate data is shown for reference (black curve). Adapted from
 447 Ref. 79.

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450 Figure 4. Scenarios of acclimatization to warm and/or cold temperatures. Panel (a) corresponds to a
 451 scenario with only decreased exposure to warm temperatures, while in panel (b) the sensitivity to cold
 452 temperatures is also increased. Acclimatization is expressed as the shift along the temperature axis of the
 453 temperature-mortality relationship by a fraction ($0 \leq R \leq 1$) of the increase in annual mean temperatures (ΔT).
 454 This fraction is equal to 0 (1) for a scenario with no (immediate) gain or loss of acclimatization to warmer
 455 summer or winter temperatures, respectively. Panels (c) and (d) correspond to the projections of annual
 456 mortality for western Europe according to these scenarios of acclimatization. Adapted from Ref. 80.

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