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TITLE: Environmental Suitability of <i>Vibrio</i> Infections in a Warming Climate: An Early Warning System

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ABSTRACT:

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et al. 2002). For example, following Hurricane Katrina in the United States in 2005, there were 22 new cases of Vibrio illness, with five deaths, due to V. vulnificus, V. parahaemolyticus, or nontoxigenic V. cholera (CDC 2005). These infections were predominantly present in men over 50 y of age with underlying liver and immune-competency issues. In all European countries, cholera infection due to Vibrio cholerae is a reportable disease, but other Vibrio infections are not reportable in all countries. In some countries, screening of patients with diarrheal diseases is only done in travel-related cases. Consequently, accurate estimates of Vibrio spp. infections are not available in Europe, although outbreaks of Vibrio-associated illnesses have been reported from a number of European countries (Le Roux et al. 2015). The sea surface temperature (SST) of enclosed bodies of water and estuaries has increased more rapidly as a result of climate change than that of oceans (European Environmental Agency 2012). Elevated SST in brackish water provides ideal environmental growth conditions for Vibrio species (Johnson et al. 2012; Julie et al. 2010; Kaspar and Tamplin 1993; Motes et al. 1998; Pfeffer et al. 2003; Vezzulli et al. 2013; Whitaker et al. 2010). These conditions can be found during the summer months in areas of water with moderate salinity such as the Baltic Sea, Chesapeake Bay in the northeast United States, and the East China Sea around Shanghai. For example, the number of Vibrio cases around the Baltic Sea has been found to increase in line with a rise in SST (Baker-Austin et al. 2012); during the summers of 1994, 2003, 2006, 2010, and 2014 elevated SST across much of the Baltic Sea was associated with reported Vibrio-associated illness (Andersson and Ekdahl 2006; Baker-Austin et al. 2016; Dalsgaard et al. 1996; Frank et al. 2006; Lukinmaa et al. 2006; Ruppert et al. 2004). In contrast, open ocean environments do not usually provide suitable growth conditions for these bacteria due to their high salinity, low temperature, and limited nutrient content. Monitoring is critical, given the projected increase in SST in the future and the potential severity of Vibrio infections (Lindgren et al. 2012). More specifically, monitoring the environmental context for such infectious diseases can serve as an early warning system for public health (Nichols et al. 2014; Semenza et al. 2013; Semenza 2015). The European Centre for Disease Prevention and Control (ECDC) developed a quasi?real-time, Web-based platform, the ECDC Vibrio Map Viewer, to monitor environmentally suitable marine areas for Vibrio growth (ECDC 2016). This paper presents evidence from marine environments around the world showing that the ECDC Vibrio Map Viewer can detect environmental changes that are of public health importance. It relates environmental data from the ECDC Vibrio Map Viewer to epidemiological data and, more specifically, assesses the relationship between SST in the Baltic Sea and Vibrio infections in Sweden. It also presents the risk of Vibrio infections along the Swedish Baltic Sea coast in relation to increasing SST due to climate change under RCP scenarios 4.5 and 8.5.MethodsECDC Vibrio Map ViewerThe ECDC Vibrio Map Viewer (https://e3geoportal.ecdc.europa.eu/SitePages/Vibrio%20Map%20Viewer.aspx) displays coastal waters with environmental conditions that are suitable for Vibrio spp. growth internationally (Figure 1). It is based on a real-time model that uses daily updated remotely sensed SST and sea surface salinity (SSS) of coastal waters (see below) as inputs to map areas of high suitability for Vibrio spp. that are pathogenic to humans (Copernicus Marine Environment Monitoring Service 2016; NOAA 2016). SST and SSS are two key environmental factors that influence the number of infections, based on a model developed by Baker-Austin et al. (2012). For the Baltic Sea, SSS demarcates the regions suitable for Vibrio infections (Copernicus Marine Environment Monitoring Service 2016) and SST serves as a risk predictor (NOAA 2016). Salinity in coastal waters is strongly modified by rainfall and, in turn, by river flow; the model uses a threshold of 26 practical salinity units (PSU) for SSS and 18°C for SST. The nominal spatial resolution of the output is 5km. The daily suitability index ranges from zero to a maximum that is determined by the highest SST value. Thus, the output detects coastal areas with environmental conditions suitable for Vibrio species that can cause infections in humans. These fields, which are estimated on a daily basis by the National Oceanic and Atmospheric Administration's (NOAA) Atlantic OceanWatch node at the Atlantic Oceanographic and Meteorological Laboratory (AOML) in Miami, Florida, are integrated within the ECDC Vibrio Map Viewer, which is the point of access in the Baltic region. Figure 1. ECDC Vibrio Map Viewer: environmental suitability for Vibrio spp., July 2014, Baltic Sea. Source: Reproduced from https://e3geoportal.ecdc.europa.eu/SitePages/Vibrio%20Map%20Viewer.aspx, © European Centre for Disease Prevention and Control. Environmental DataIn the Baltic Sea, low-salinity areas delineate the areas suitable for the occurrence of Vibrio infections, whereas SST serves as a risk predictor (Baker-Austin et al. 2012); however, the influence of SST and SSS on the environmental suitability for Vibrio growth can be extrapolated to other regions of the world to obtain global risk estimates. The ECDC Vibrio Map Viewer was designed to delineate retrospective, current, and short-term forecasts of environmental suitability at a global scale, which requires obtaining reliable SST and SSS, especially in coastal regions where human exposure is more likely to occur (Figure 1). The global model data inputs are SST fields from remote sensing and models, as well as SSS from models, in situ data, and climatological data. The estimates for SST were obtained from a number of sources: ?USDOC/NOAA/NESDIS (U.S. Department of Commerce/NOAA/National Environmental Satellite Data and Information Service) COASTWATCH NOAA19/METOP-A/GOES-E/W MSG/MTSAT SST Blended Analysis?NOAA/NCEP (National Centers for Environmental Prediction) Global Real-Time Ocean Forecast System? Navy Coastal Ocean Model (NCOM) for the Gulf of Mexico, Caribbean, and U.S. East Coast? Operational Mercator Global Ocean Analysis and Forecast System? Iberian Biscay Irish (IBI) Ocean Analysis and Forecasting system? Forecasting Ocean Assimilation Model 7km Atlantic Margin model (FOAM AMM7)?Baltic Sea Physical Analysis and Forecasting Product?Mediterranean Sea Physics Analysis and Forecast?Black Sea Physics Analysis and ForecastSSS were obtained from the Copernicus Marine Environment Monitoring Service (2016). For retrospective studies, NOAA's Optimum Interpolation (OI) SST V2 data set provided satellite and model-interpolated daily analysis of SST in a consistent methodology back to September 1981. For the Swedish coastal counties, mean SST were spatially aggregated per county per week for the years of analysis (2006?2014) to generate time-series data sets for each coastal county. Climate change projections of SST were derived from a Coupled Model Intercomparison Project Phase 5 (CMIP5) model ensemble (r1i1p1) for the Swedish coastline aggregated by county. Time series per month for each county from 2005 through 2100 were derived. Model output was obtained for emission scenarios RCP 4.5 and RCP 8.5, representing a possible range of radiative forcing values in the year 2100 relative to preindustrial values (+4.5, and +8.5W/m2, respectively). Case DataInfections caused by Vibrio cholerae (other than serotypes O1 or O139 and Vibrio cholerae serotype O1 or O139, which are nontoxigenic) are notifiable according to the Swedish Communicable Diseases Act (Swedish Code of Statutes 2004) and include V. parahaemolyticus, V. vulnificus, and V. alginolyticus. Cases are reported to the mandatory notification system at the county medical office and at the Swedish Public Health Agency. We obtained a listing of all Vibrio infections from 2006 through 2014 with clinical and laboratory confirmation from the Swedish Public Health Agency (Folkhelsomyndigheten 2016). The listing included information on county, statistical date and onset of disease, type of infection, Vibrio species, serotype, transmission pathway, sex, and age group of each case. For reasons including consistency in reporting and data completeness, we used data for the period 2006 through 2014 for our analysis. A total of 117 cases were reported for the period from June 2006 through October 2014, of which 111 occurred in coastal counties with a possible link to SST. Thus, being in close proximity to the Baltic provides the opportunity for exposure to coastal water both for case and control times. However, 30 of these cases had no precise place of infection and 25 cases had no date of onset of disease, and these cases were not included in the analysis. Statistical Analyses The variables of the 56 Vibrio cases for 2006?2014 were subjected to descriptive statistics and frequency analysis. Because changes in SST occur intermittently, have a short induction time and a transient effect (Vibriosis), a case-crossover study design was chosen to assess the association between SST and Vibrio infections. The SST exposure status (mean SST, spatially aggregated per county and per week) of the Vibrio infection at the time of the Vibriosis onset was compared with the distribution of the SST exposure status for that same Vibriosis case in earlier/later periods. This approach assumes that neither exposure nor confounders change over the study period in a systematic way. Thus, a time-stratified approach at the individual level was used for control days to contrast with the events. An advantage of using such a time-stratified case-crossover design is the automatic adjustment for individual non-time varying factors; these can risk introducing confounding bias in epidemiological studies if not adjusted for. Further, the time-stratified approach used control events before and after the event date for each individual Vibrio infection in the same area. We used 2, 4, and 6 wk as the time window between event data and the control days, both before and after the event. This adjusts for unknown temporal confounders and controls for seasonal influences not related to the seasonality of SST as the primary exposure variable. The weekdays of the dates of the weekly county means of the SSTs were restricted to Mondays, but the date of infection was for any date. Thus, in order to match the date of infection with its corresponding SST, Tuesday to Thursday were referred to the preceding Monday, whereas Friday to Sunday were referred to the following Monday. For analysis, a data set with the event itself and control events 2, 4, and 6 wk before and after the event was created. A time series with SST county means from 1 to 8 wk before the event and the controls was added. We used a conditional logistic regression model to ascertain a relationship between SST and Vibrio infection and to derive an exposure?response curve for the relationship between the odds ratio of Vibrio infection and SST. We refer to the odds ratio analogously to relative risk in this study due to the low probability of disease events. We studied the relationship between Vibrio infections and SST using natural cubic splines (4 degrees of freedom) and for different lead times of exposure up to 4 wk before disease occurrence. We identified a piecewise linear model with a knot of SST at 16°C for the final model. We used the computed case-crossover exposure? response relationship to project how the seasonal window of transmission would change in each of the counties. We used projections of SST data from a global circulation model from CMIP5 for each month in the time period from 2006 through 2099 for each county. Months with elevated risk were categorized as potential transmission months and aggregated as average per decades. The annual maximum elevated risk month was averaged to a change of transmission intensity per decade. Relative risk estimates are presented using the year 2016 as the baseline and describe changes due to SST from there onward. We used also CMIP5 sea surface temperature projections for the RCP projections to illustrate differences in the projected SST

between RCP 8.5 and RCP 4.5 for August 2050. We computed the surface area [in kilometers squared (km2)] of the Baltic Sea that is environmentally suitable for Vibrio growth for RCP 4.5 and RCP 8.5, from 2010 through 2060, by month.ResultsIn July 2014, SST in the Baltic Sea reached record highs and the ECDC Vibrio Map Viewer detected environmentally suitable areas for Vibrio spp. (Figure 1). High Vibrio suitability was detected in the northern and the southern parts of the Baltic Sea in mid-July, and this extended to the entire Baltic Sea by the end of the month. The annual frequency of total Vibrio cases notified in Sweden from 2006 through 2014 is presented in Figure 2. A peak in cases was observed in 2006 and in 2014, compared with other years. Vibrio infections other than CTX (cholera toxin)-producing V. cholerae (O1 or O139) reported in Sweden, included in the case-crossover analysis, are listed in Table 1. The majority of infections were detected in the ear (50%), but wound infections (28%) and septicemia (20%) combined constituted almost half of all infections. Only a small fraction of the samples found pathogens in stool, saliva, or urine (2%). A time series analysis of the site of infection did not reveal a time trend in Vibrio infections, with the exception of wound infections that indicated an increase. Almost one-third (30%) of the cases were ?60y of age, 25% were 10?19 y of age, 25% were 20?59 y of age, and 20% were ?9y of age. The SSTs along the Swedish coast were interpolated for the study period (2006?2014). An exposure?response relationship was estimated with a case-crossover study; additional non-disease (no Vibrio infections) time periods with the corresponding SST were selected as matched control periods for each Vibrio infection. The estimated exposure?response relationship for Vibrio infections in response to SST is shown in Figure 3. At the threshold of 16°C SST, with a lag of 2 wk, the relative risk (RR) was 1.14 [95% confidence interval (CI): 1.02, 1.27]. The relationship between Vibrio infections and SST was statistically significant (p=0.024), and the estimated risk increased successively beyond a threshold of 16°C SST. However, that relationship did not hold at lower SST. Case data were available with a statistical date and a date of onset of disease. The date of onset of disease correlated to the SST of the same week and with lags up to 2 wk, whereas the statistical date, which is the first date when the case was reported to the national notification system for the cases correlated best with lags between 2 and 4 wk.Figure 2. Annual frequency of total Vibrio infections notified in Sweden, 2006?2014.Figure 3. Exposure?response relationship of Vibrio infections in response to sea surface temperature (SST), Sweden 2006?2014. Note: Because Vibrio infections in the Baltic are relatively rare, the relative risk is used here analogously to the odds ratio. Table 1 Vibrio infections other than Vibrio cholera, included in the case-crossover analysis, reported in Sweden by site of infection, species, age, sex, region, 2006 through 2014. Table 1 lists demographic data in the first column and number of cases in the second column.Demographic dataCases (n)Male82Female35Age Mean (y)40.9 SD (y)29 Range (y)2?94Route of infection Blood20 Ear59 Feces3 Mouth1 Urine1 Wound33Vibrio spp. V. alginolyticus13 V. parahaemolyticus14 V. vulnificus3 V. cholerae (not CTX producing)48 Vibrio species (not agglutinating V. cholerae)39Counties Blekinge6 Gotland1 Gävleborg6 Halland9 Jämtland1 Jönköping4 Kalmar3 Kronoberg5 Skåne27 Stockholm21 Uppsala4 Värmland3 Västerbotten3 Västernorrland3 Västra Götaland15 Örebro3 Östergötland3Climate change projections for SST under the RCP 4.5 and RCP 8.5 scenarios for the 21st century were used to estimate the relative risk of Vibrio infections in the future. A global comparison of the SST between RCP 4.5 and RCP 8.5 for August 2050 is shown in Figure 4A, which illustrates a general warming overall, but also regional cooling in certain locations, such as the Baltic Sea (Figure 4B). The monthly projection of SST suitability for Vibrio in the Baltic Sea up to 2060 is provided in Figure 5. A marked upward trend is observed for SST during July, August, and September but even more so during the months immediately prior to and after the summer (June and October). Figure 4. Difference of sea surface temperature (SST) between RCP 4.5 and 8.5 for August 2050: (A) global and (B) regional.Note: Climate model for RCP projections: CMIP5 SST projection that uses various models (86 total). The figures were created using a data set from a contribution to GEOSS Data-Core (GEOSS Data Collection of Open Resources for Everyone), as a result of the GEOWOW (GEOSS interoperability for Weather, Ocean and Water) project. Data are licensed under Creative Common CC-BY-4.0 (as defined in http://www.opendefinition.org/licenses/cc-by), which allows redistribution and re-use. Data sources: Combal 2014a, 2014b, 2014c. Difference RCP 8.5?4.5: Difference in the projected SST between RCP 8.5 and RCP 4.5 for August 2050. RCP 8.5 projections are in general warmer than RCP 4.5 ones. However, the distribution and intensity of the differences are inhomogeneous and highly variable. The values are predominantly positive but negative values are shown in the Baltic Sea during this period. Figure 5. Suitability for Vibrio based on SST in the Baltic Sea for RCP 4.5 and RCP 8.5, from 2010 through 2058, by month. Note: The figures were created using a data set from a contribution to GEOSS Data-Core (GEOSS Data Collection of Open Resources for Everyone), as a result of the GEOWOW (GEOSS interoperability for Weather, Ocean and Water) project. Data are licensed under Creative Common CC-BY-4.0 (as defined in http://www.opendefinition.org/licenses/cc-by), which allows redistribution and re-use. Data sources: Combal 2014a, 2014b, 2014c. The area suitable for Vibrio growth is projected to expand over the coming decades, particularly during June and September (Figure 6), doubling between 2015 and 2050. In July 2015, the area of risk was 140,000 km2; for scenario RCP 4.5, the area of risk would reach 309,966 km2 in July 2050 and for RCP 8.5,

317,793 km2 in July 2050. Figure 7 shows Baltic Sea areas suitable for Vibrio growth during the months of June, July, August, and September 2016 and for RCP 4.5 and RCP 8.5 in 2050. The RCP 8.5 scenario for 2050 gives a lower maximum SST than RCP 4.5 (Figure 7); although at global level, the rise in temperature is higher with RCP 8.5 (Figure 4), and at a regional level, RCP 4.5 gives higher temperatures for this particular year. The difference is significant and at some point the differences between the two models can reach up to 2°C. This discrepancy is also visible in the isotherms for the difference between 2015 and projections for 2050 under RCP 4.5 and RCP 8.5 by month (see Figure S1). Figure 6. Surface area (km2) of the Baltic Sea that is environmentally suitable for Vibrio growth for RCP 4.5 and RCP 8.5, from 2010 through 2060, by month. Note: The figures were created using a data set from a contribution to GEOSS Data-Core (GEOSS Data Collection of Open Resources for Everyone), as a result of the GEOWOW (GEOSS interoperability for Weather, Ocean and Water) project. Data are licensed under Creative Common CC-BY-4.0 (as defined in http://www.opendefinition.org/licenses/cc-by), which allows redistribution and re-use. Data sources: Combal 2014a, 2014b, 2014c. Figure 7. Environmental suitability for Vibrio based on maximum SST for 2016, for 2050 with RCP4.5, and for 2050 with RCP8.5, for June, July, August, and September. Note: Environmental suitability fields in the Baltic Sea during June, July, August, and September: low-salinity areas delineate the region suitable for the occurrence of infections, whereas SST serves as a risk predictor. The left column shows the fields estimated for the year 2016. The center and right columns show the projected suitability index (SI) for the year 2050, under RCP 4.5 and RCP 8.5, respectively. In both cases, there is an important increment in the mean values of the SI (SI>10) when compared with the year 2016. The figures were created using a data set from a contribution to GEOSS Data-Core (GEOSS Data Collection of Open Resources for Everyone), as a result of the GEOWOW (GEOSS interoperability for Weather, Ocean and Water) project. Data are licensed under Creative Common CC-BY-4.0 (as defined in http://www.opendefinition.org/licenses/cc-by), which allows redistribution and re-use. Data sources: Combal 2014a, 2014b, 2014c. The change in relative risk (%) for Vibrio infections in comparison with 2015 is illustrated in Figures 8 and 9 for the coastline of Sweden for RCP 4.5 and RCP 8.5. A marked increase in the relative risk was predicted beyond the year 2039 for both scenarios and, toward the end of the 21st century, the change in relative risk was particularly pronounced for the RCP 8.5 scenario. Figure 8. Change in relative risk (%) of Vibrio infections associated with climate change scenario RCP 4.5, 21st century. Figure 9. Change in relative risk (%) of Vibrio infections associated with climate change scenario RCP 8.5, 21st century. Potential transmission months, defined by an elevated risk for Vibrio infections based on the SST, were aggregated as averages per decades (see Figures S2 and S3). The transmission season is and will be longer in the southern part of Sweden compared with the northern part. Under climate change scenarios RCP 4.5 and RCP 8.5, the number of months with risk of Vibrio transmission increases; the seasonal transmission window expands, with markedly higher increases of months with transmission for the high emission scenario RCP 8.5. However, the impact of climate change becomes more prominent in the northern part after the year 2039 when the transmission season reaches the current levels of southern Sweden. Discussion In July 2014, the ECDC Vibrio Map Viewer detected highly suitable conditions for Vibrio infections in the Baltic Sea (Figure 1) and the mandatory notification system at the Swedish Public Health Agency reported a historic peak of Vibriosis cases for 2014 (Figure 2). We demonstrate with a case-crossover study that the reported Vibrio infections are related to these favorable environmental conditions; we found a pronounced exposure?response relationship between SST and Vibrio infections (Figure 3). Climate change projections indicate that the risk for Vibrio infections will increase in the 21st century: The transmission season will be expanded and the number of months with risk of Vibrio transmission will increase, particularly in the northern latitudes of the Baltic Sea. SST in the Baltic Sea is projected to increase by 4?5°C over the next decades due to climate change. The 5-d forecasting function available on the ECDC Vibrio Map Viewer can serve as an early warning system for Vibrio infections in the Baltic Sea (Figure 1). Currently, ECDC monitors the environmental suitability for Vibrio infections in the Baltic Sea with the ECDC Vibrio Map Viewer on a weekly basis and, during the transmission season, publishes the findings in its Communicable Disease Threat Reports (CDTR). This enables public health authorities to take action, such as issuing alerts to the public or information to immunocompromised individuals or even beach closures. The European Environmental Agency provides information on bathing water quality, based on actual measurements of bacterial contamination (intestinal enterococci and Escherichia coli) of recreational water sites (European Environmental Agency 2016), whereas the alerts from the ECDC Vibrio Map Viewer are based on estimates of environmental suitability for Vibrio infections, not actual risk because no exposure data are available for such an assessment. Globalization, through international travel and trade, is an important driver of emerging infectious diseases (Semenza et al. 2016), including virulent Vibrio strains, and can synergistically interact with other drivers such as climate change (Semenza and Menne 2009). A new serotype of V. parahaemolyticus (O3:K6) has emerged in Asia and has spread rapidly to South America (González-Escalona et al. 2005; Martinez-Urtaza et al. 2008). The pandemic expansion of this strain is associated with large-scale food-borne disease outbreaks (Yeung et al. 2002). Other virulent V.

parahaemolyticus strains (O4:K12 and O4:KUT) have recently

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