BD2K analytics reveals the Zika virus epidemic as only one of multiple factors contributing to year-over-year 28-fold increase in microcephaly incidence

Darryl B. Hood, Ph.D.,
Associate Professor
Division of Environmental Health Sciences
College of Public Health

Conflict of Interest Statement
The author declares no conflict of interest
Outline of Presentation

Introduction: Place! (zip code → census tract → census block)

US EPA STAR Collaboration

Public Health Exposome framework and BD2K analytics

Exemplar: Brazil and Zika
  • Methodology
  • Results
  • Conclusions
  • Discussion
Place matters with regard to health care disparities and disparate health outcomes

Exposure to Chemical & Non-Chemical Stressors

Social Environment
- Race/Ethnicity
- Education
- Income/Employment
- Health Insurance
- Culture

Physical Environment
- Air
- Water
- Soil

Policy Environment
- Federal
- State
- Local
- Laws & regulations

Built Environment
- Live
- Work
- Play
- Pray

Moderating Factors
- Nutrition, Literacy,
- Positive parenting
- Social networks
- Safe neighborhoods
- Personal behaviors

Public Health Exposome Framework
w/ BD2K Analytics

Population Level Disparities
- Cardiovascular
- Diabetes
- Cancer
- LBW, PTB, IM
- m-ZIKV(+/-)

Disparate Health Outcomes
- Morbidity/Mortality
- Immune System/Immuno-suppression
- Neuro-cognitive developmental delay
- Longevity and other chronic diseases

Behaviors
- Smoking
- Alcohol
- Drugs
- Diet/Nutrition
- Consumer Products

Omics
- Metabolomics
- Transcriptomics
- Microbiomics
- Epigenomics
- Genomics

GLOBAL SIGNIFICANCE, LOCAL IMPACT
Public Health Exposome framework

**Public Health Exposome**
- Physical Environment
- Built Environment
- Social Environment
- Policy Environment

**COMMUNITY**
- Community Assets
- Social Supports
- Access to Care
- Pre-Existing Conditions

**INDIVIDUAL**
- Genes
- Epigenetics/Omics
- Stage of Development
- Psychosocial Makeup
- Behaviors

**LIFESPAN**
- Conception to Death
- **MODERATING FACTORS**
  - Community Assets
  - Social Supports
  - Access to Care
  - Pre-Existing Conditions

**SPACE & PLACE**
- **SOUTHERN GATEWAY COMMUNITIES**
  - Stambaugh-Elwood Neighborhood (SE)*
  - Reeb-Hosack Neighborhood (RH)*
  - Innis Gardens Village Neighborhood (IG)
  - Merion Village Neighborhood (MV)
  - Vassor Village (VV)
  - Hungarian Village (HV)
  - Near East Neighborhoods (43203)

* Supervised and unsupervised clustering, parametric and non-parametric, combinatorial algorithms and paraclique analysis
BD2K analytics to interrogate significance of “Place” in high-risk census tracts

Environmental Data

Domain Knowledge

Combinatorial Algorithms

Supercomputer Platforms

Understanding Health Disparities in the Context of the Exposome

PHE Tool Chain

Data Acquisition and Curation

Organization and Preprocessing

Feature Selection

Spectral Thresholding

Unweighted Graphs

Graph-Theoretical Decomposition

Dense Subgraphs

Latent Factor Extraction

Positive Factors

Statistical Interpretation

Testable Hypotheses

Validation Studies

Translation into Practice

Environmental and Public Health Policy
BD2K analytics to interrogate significance of “Place” in high-risk census tracts

- **Secondary Environmental Data Sets**
- **Primary Environmental Data Sets**

  - **Non-Pairwise Associations (Bayesian networks)**
  - **Directed Graphs**
  - **Weighted Graphs**
  - **Supervised Groups Analysis (Multivariate Network)**
  - **Global Analysis Between Theoretical Constructs (Network Shrinkage)**
  - **Local Analysis within Theoretical Constructs**

  - **Heterogeneous Data**
  - **Pairwise Associations (Correlation Matrix)**
  - **Unweighted Graphs**
  - **Unsupervised Community Search (Dense Subgraphs)**

  - **Exploratory Analysis**
  - **Testable Hypotheses**
  - **Validation Studies (Model Curation)**

  - **Input to Environmental & Public Health Policy**
A network analysis of the incidence pattern of microcephaly in the context of Zika Virus Infection

Authors: Myriam Patricia Cifuentes1,2, Clara Mercedes Suarez2, Ricardo Cifuentes*, Nathan Doogan2, Noel Malod-Dognin3, Sam Windels1, Jose Fernando Valderrama4, Darryl B. Hood1, Nanasia Brumij3

Affiliations:
1Department of Mathematics, College of Sciences, Universidad Antonio Nariño, Colombia.
2Division of Environmental Health Sciences, College of Public Health, The Ohio State University, U.S.A.
3Maestria en Salud Pública, Universidad Santo Tomas.
4Universidad Militar Nueva Granada.
5Department of Computer Science, University College London, UK.
6Sub-directorate of Transmissible Diseases, Ministerio de Salud, República de Colombia.
Figure 1. Geographic distribution of ZIKV infection did not match with microcephaly outbreaks during the 2015-2016 ZIKV epidemic.

...alternative hypotheses as to other determinant factors that explain how the built, natural, physical and social environment interact with...
Test the hypothesis that multiple factors are associated with microcephaly incidence positive for Zika infection (m-ZIKV+).

1,810 cases of m-ZIKV+ and during 2016
3,924 cases of m-ZIKV+ during 2016
5,734 microcephalic babies in one year
117,326 low birth weight (LBW) cases
863,153 births (B)

Characterize specific patterns of associations with multiple factors, and contrast that pattern with the patterns of associations with those factors that were exhibited in three types of Controls:

1) microcephaly incidence negative for Zika infection (m-ZIKV-),
2) Low Birth Weight (LBW, indicator of infant morbidity), and
3) Births (B, as a proxy for healthy newborns)

METHODOLOGY

Collected and curated public frequency data to calculate all controlled statistical associations among 382-variables describing 16-determinant factors, incidence of concurrent health outcomes, and m-ZIKV+ surveillance from 5,565 municipalities in Brazil.

Comparative Network Inferential Analysis
Table 1. Determinants of health and health outcomes related to microcephaly attributed to ZVI included in the model. For each determinant are included Cronbach alpha values. [0.70 and above is good, 0.80 and above is better, and 0.90 and above is best].

<table>
<thead>
<tr>
<th>Scale</th>
<th>Determinant</th>
<th>Summary of variables in each determinant</th>
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<tbody>
<tr>
<td>Critical determinants</td>
<td>Governance</td>
<td>Governance is depicted as the formalized convergence of diverse social factors of decision making, such as municipal planning agencies, mechanisms for empowering citizens and involvement in high-level policy agendas (12).</td>
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<td></td>
<td>Macroeconomic policy</td>
<td>Variables describe the balance through economic impositions and fostering and the resulting economic inequalities in population by Gini and Theil indices (2, 12-14).</td>
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<td></td>
<td>Social policy</td>
<td>Variables relating to social support in municipalities through proxies of ZEIS (Zonas Especiais de Interesse Social) for low income housing and inter-institutional social support and development (2, 12-14).</td>
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<tr>
<td></td>
<td>Public policy</td>
<td>Variables describe diverse instruments such as laws and regulation that stabilize general public policies on environment, land use, urban settlement, development and housing, economy and transportation.</td>
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<td>Culture and social values</td>
<td>Variables relating to institutional concerns of cultural and educational affairs in municipalities (12).</td>
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<td>Demographic/Epidemiologic conditions</td>
<td>Population age pyramid according to the 2010 census and 2015 population estimate for municipalities. Institutional concerns of health and sanitation in municipalities (12, 15).</td>
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<td>Social determinants</td>
<td>Income</td>
<td>Population percent and income distribution between rich, vulnerable, poor and poorest populations, and for workers and unemployed. We also included the mean income by race, and the GDP per capita GDP and the human development index (HDI) and its income dimension in municipalities (14, 16).</td>
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<td></td>
<td>Education</td>
<td>Attainment and enrollment by academic level (primary and middle), literacy by race, and gender and age thresholds, and the expected years of study. We included the dimension of “education” of HEI (14).</td>
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<td>Occupation</td>
<td>Participation in the workforce and unemployment, differentiated by race, educational attainment and work sector, and commuting (12, 14, 15).</td>
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<td>Social Class</td>
<td>Social class by individuals and households located in agglomerates qualified as subnormal, and variables labeling social vulnerability (15).</td>
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<td></td>
<td>Race/Ethnicity</td>
<td>Distribution by Brazil’s racial groups (2, 12, 13).</td>
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<td></td>
<td>Social Networks/Sociocultural Circumstances</td>
<td>Civil status, people and children in households supported by people without education of who are vulnerable, and dependency ratio (12, 14, 16).</td>
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<td></td>
<td>Biological Factors</td>
<td>Population distributed by sex, and women population in fertility age groups, fertility rate, infant female and male populations, life expectancy, longevity and aging rate. Longevity dimension of the Human Development Index (16).</td>
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<td>Childhood Development</td>
<td>Negative approach by Low Birth Weight (LBW) and less than 1 year of age who remained childless (12, 13).</td>
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<td>Material Circumstances</td>
<td>Dwelling material, availability and access to water/flush house pipe water, sewage system, and waste disposal. Access to electricity, vegetation distribution and land use. Potential exposure to agro-toxic by agricultural use or residue disposal. Rapid assessment of indicators for Adequacy (Velocimetro Rápido de Indicadores de Adequados (VRAI)) (12, 17), Low Income Rate Assistance.</td>
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<td>Health System (5-974)</td>
<td>Variables of investment (national and local) and performance of Brazil Health System in municipalities, all level care and normal delivery, primary and higher levels of care coverage and public health actions. We included as one of the main public health actions a very detailed documentation of vaccinations, number of doses (as a proxy of the strength of this intervention) and coverage (width of intervention over beneficiary population) for 2015 and 2016 (15, 16).</td>
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<td></td>
<td>Vectorborne Diseases</td>
<td>Severe dengue, Malaria and Chagas disease cases (15, 16).</td>
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<td></td>
<td>Other Health Results</td>
<td>Infant and childhood mortality, and incidence rate of congenital syphilis. Different poisoning incidence according to locality of exposure, notification and residence (18). Place of exposure indicative of contact with toxic substances, while place of residence and notification correspond to the administrative process.</td>
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<td>Microcephaly Surveillance</td>
<td>Surveillance of microcephaly incidence, including incoming and investigated microcephaly cases, and confirmed/documented ZVI cases during the first trimester of 2016 (19).</td>
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<tr>
<td></td>
<td>Stillbirths Surveillance</td>
<td>Surveillance of stillbirth incidence, including incoming and investigated stillbirth cases, and confirmed/documented ZVI cases (19).</td>
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</table>
Methodology (Continued)

- To control associations from spuriousness and confounding, squared higher order partial correlations (pcor²) were used as proxies for effect size, complemented by zero-order correlations (zcor) and partial correlations (pcor), each with the corresponding significant p-values evaluated after correction for multiple comparisons.

- **Macroanalyses** compared subnetwork structures by statistical tests between distributions of their network indices and by advanced network structural methods of graphlet distance.

- **Microanalyses** assessed the details explaining the differences by comparing the fingerprints of all aligned subnetworks.

- **Subnetwork fingerprints corresponded to visualizations of ordered weighted associations between matching pairs of variables in each subnetwork.**
Context networks derived from Exposome framework and BD2K analytics demonstrating associations of multiple determinant factors with Zika Virus Disease incidence in Brazil's municipalities during the 2015-2016 outbreak. Groups of variables within each determinant factor are shown.

Four colors show strongest positive partial correlations (dark blue), strong (green), negative strongest (dark red), and strong (light red) partial correlations among variables/nodes. A, shows the full network, including labels. B, corresponds to the threshold network by graphlet optimally far from random network. C, corresponds to threshold network clustering coefficient-based optimally far from random network. (Cifuentes et al., 2021)
Evaluated the patterns of factors associated with case and control phenomena by extracting the corresponding subnetworks. The case subnetwork included all interdependent nodes directly linked to m-ZIKV+ incidence (Figure 2. Panel A). Control subnetworks included all nodes directly linked with m-ZIKV- incidence (Figure 2. Panel B), LBW (Figure 2. Panel C), and Births (B) (Figure 2. Panel D).

Figure 2. General pattern of factors associated with microcephaly is unspecific for m-ZIKV+

Extracted Subnetworks (A-D) from the 0.65 threshold context network (Fig. 1) by the method of $k=1$-neighbors.
Figure 2. General pattern of factors associated with microcephaly is unspecific for \( m\text{-ZIKV}^+ \)

- Oscillation amplitude of control subnetworks pcor\(^2\) show the smallest differences between \( m\text{-ZIKV}^+ \) and \( m\text{-ZIKV}^- \)
- Moderate differences between \( m\text{-ZIKV}^+ \) and LBW (indicator of infant morbidity)
- Robust differences between \( m\text{-ZIKV}^+ \) and B (as a proxy for healthy newborns)
- Flat red line indicates no connections.
Figure 3. Factors that explained the non-specific pattern of associations of microcephaly incidence positive for Zika infection (m-ZIKV+)

- In general agreement with the recent work reported by Brady et al., 2019, comparisons by this method suggested that the patterns of factors associated with case m-ZIKV+ and control m-ZIKV- subnetworks were analogous.

- Among the three, intermediary factors had a slightly higher influence.

- By contrast, for the LBW-subnetwork, factors in the social structure and intermediary scales were significant.

- For the B-subnetwork, factors in all three scales had low-to-moderate effects.

Legend: Heat bands summarizing patterns of association of each subnetwork. Values of zcor, pcor, pcor² are visualized by color gradients that are analogous to single columns of heat maps. The descending ordered pcor² within determinants of ZIKV+ is the reference pattern (first column, teal shade).

Panel A, bands by the three broad scales of determinants.

Panel B, Bands by Determinant factors.

Panel C, Bands by single variables within factors.
Figure 4. Factors in the scale of structural determinants.

- In the microcephaly incidence positive for Zika infection (m-ZIKV+) subnetwork, links with race/ethnicity and social class had the highest avg-pcor².

- The factor of social class mainly included variables describing vulnerability.

- Occupation’ factor showed a moderate avg-pcor² by nodes of ‘labor force,’ ‘unemployment proportion’ (general and by race), and ‘unemployment in the environmental field’ as the only specific occupational sector involved.

- Conversely, ‘income’ and ‘education’ factors had very low avg-pcor². Inside the income factor, ‘mean income’ and ‘Theil index for work revenues’ had high pcor², while ‘income of 20% richest’ and ‘per-capita GDP’ had moderate pcor².

- Inside the education factor, only ‘enrollment of 5-6year-old’ and ‘illiteracy’ were associated respectively, by moderate and low pcorr². Minor differences of the m-ZIKV-subnetwork were due to links with ‘unemployment in the construction sector’ inside the occupation factor, and linked absence with ‘per-capita GDP’ in the income factor (Fig. 4B).
Figure 5. Factors in the scale of structural determinants.

In the control LBW-subnetwork, the determinants of race, social vulnerability, and occupation in the structural scale stood out based on avg-pcor².

Within the race determinant White, mixed, and Black had the highest pcor²; all social vulnerability variables were linked except ‘woman head of family’. These association patterns inside each of the determinants were similar to those in the microcephaly incidence positive for Zika infection (m-ZIKV⁺) subnetwork.

In the control B-subnetwork, the determinant of race also had the highest avg-pcor², but, in contrast to the associations in the m-ZIKV⁺-subnetwork, education, income, and occupation were relevant. Per capita GDP, illiteracy (determined without reference to race), primary school enrollment, participation in the labor force by members of yellow and indigenous races, and self-employment were remarkable nodes with high pcor².

While the LBW-subnetwork and the B-subnetwork have significant associations with a number of the same structural determinants, the most obvious observation is the fact that those associations have opposite signs for each subnetwork, respectively.
Figure 6. Factors of the intermediary scale.

- These factors convey underlying social stratification of structural factors, by determining differences in exposure and vulnerability to health-compromising conditions and includes material, psychosocial, behavioral, and biological factors. Among the three scales, the intermediary scale contributed the most to the microcephaly incidence positive for Zika infection (m-ZIKV+) subnetwork (Fig. 4B), and all its factors were associated with that subnetwork.

- ‘Childhood development’ had the highest avg-pcor² of the factors, mainly due to the value of this factor in the LBW-subnetwork. Similarly, the avg-pcor² of the intermediary scale in the LBW-subnetwork was the highest due to the contributions of all determinants with main roles in the ‘undernourishment’ node and factors of ‘social relationships’ and the ‘health system.’ In the B-subnetwork conversely but as expected, association with problems of ‘childhood development’ was absent.

- The factor of social relationships includes variables about marital status. Most marital status variables had associations in the m-ZIKV+-subnetwork.

- These data support the view that different types of family relationships (protective/stable, unstable and/or weak) offer a similar substrate to cases of microcephaly and LBW, but not to cases of normal birth.
Involves access to care and health interventions. This factor had similar avg-pcor$^2$ in case and control subnetworks, however the opposite sign of avg-pcor in the B-subnetwork that comports with health care having a different role for healthy and ill populations.

Immunizations are recognized preventive health measures and the focal point w/r re-emergence of infectious diseases that will threaten populations. The (immunity) interventions are not straightforward and encompass diverse results from positive (cross-immunity) to negative (sporadic secondary undesired effects).

In the control LBW-subnetwork, a wider variety of customary vaccinations during 2015 and 2016 were associated with a with lower pcors$^2$.

Broader pattern of vaccinations was present in B-subnetwork with almost all pcors with opposite signs. This grounded the interpretation of other subnetworks and for discerning the potential protective role of vaccinations.

For other health care interventions, the connection between ‘prenatal care’ and microcephaly incidence positive for Zika infection (m-ZIKV$^+$) was the strongest and pcors$^2$ successively decreased in the m-ZIKV$^+$-subnetwork to the LBW-subnetwork to the B-subnetwork.
Environmental Policies common to both types of microcephaly

Differences in Macroeconomic Indicators between both types of microcephaly

Unequal distribution of municipal income between positive and negative m-ZIKV.

Inverse proportional relationship of m-ZIKV+/- in higher income populations.

Differential involvement of white couples and late fertile age women populations showed potential biological vulnerabilities.

There is an associated relationship of ZIKV-related microcephaly with mosquito breeding but not with mosquito populations.

Because these associations are even higher with LBW, this observation should dampen the enthusiasm for the effectiveness of this intervention.

The collective relationships presented for both types of microcephaly is an emergent factor to explain non-ZIKV-related microcephaly.
Comparative network inferential analysis of patterns of factors associated with Zika virus infections in Brazil during 2015-2016 coinciding with a microcephaly epidemic identified multiple contributing determinants that advances our understanding of the effects of exposures to chemical and non-chemical stressors in the built, natural, physical, and social environment.

The results revealed latent factors, their central roles and convergence to suggest that effects related to ZIKV-microcephaly incidence in Brazil were not specific to Zika infection and were common to both types of microcephaly.

Diagnostic failure to discern Zika infection during the epidemic likely explains this result. This suggests underestimation of the size of Brazil’s ZIKV+ microcephaly incidence. Alternatively, assuming that diagnostic uncertainty similarly affected both groups makes evident that microcephaly is a complex event where multiple causes and mediators converge.

Zika diagnostic tests deserve a general inclusion in antenatal screenings, even more, if multiple modes of transmission increase uncertainty about infection risk. Above all, improving diagnostic tests is critical.

Public health interventions include the spread of agrochemicals to control mosquito populations. An extensive presence of mosquitoes implies widespread exposure to these agrochemicals. Therefore, in addition to the links intuitively found between Zika infection, its vector, and m-ZIKV+, a link between the co-occurrence of this nonselective exposure and microcephaly is suggested. These data are in support of molecular data on exposures to the insecticide pyriproxyfen with dampening of neurodevelopmental processes particularly in areas with ZIKV prevalence.
Context networks derived from Exposome framework and BD2K analytics demonstrating associations of multiple determinant factors with Zika Virus Disease incidence in Brazil’s municipalities during the 2015-2016 outbreak. Groups of variables within each determinant factor are shown.

Four colors show **strongest positive partial correlations** (dark blue), **strong** (green), **negative strongest** (dark red), and **strong** (light red) partial correlations among variables/nodes. A, shows the full network, including labels. B, corresponds to the threshold network by graphlet optimally far from random network. C, corresponds to threshold network clustering coefficient-based optimally far from random network. (Cifuentes et al., 2021)
Thank you!

Twitter reacts to the Bears selection of Justin Fields!

@DhooB
OSU Buckeye Hood Family: We are elated because we can go see Justin Fields and the Chicago Bears when we are there on weekends during football season.

@DhooB
We will be visiting our daughter Alexis who is a PGY1 resident at U of Chicago and coupling that to football makes for great weekends in the Windy City!
Ohio State University & Meharry
Paul Juarez
Patricia Cifuentes
M. McCallister
Tongwen Zhang
George Jules
Raina Rhoades
Aramandla Ramesh
Habibeh Khoshbouei
Jing Bin Wang

UT Knoxville- Mike Langston

FAMU
F. Close and S. Stokes

Vanderbilt
Ford Ebner
Steven Lloyd
Miki Aschner
FP Guengerich

USC
Pat Levitt
Dan Campbell

Auburn
M Chris Newland

TAMU

EPA-STAR
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NCRR-RRO3032-35
T32MH065782

Nancy Lurie Marks Foundation
&
Simons Foundation Autism Research Initiative

GLOBAL SIGNIFICANCE, LOCAL IMPACT
LITERATURE CITED


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<table>
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<tr>
<th>SCALE</th>
<th>avg-pcorr at Scale level</th>
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