**Antimicrobico-resistenza: cure e ambiente #7**

***Nulla è costante, se non il cambiamento***

# Impatto del clima sui batteri di interesse medico

Simona Barnini, AOUP

Credit: Pedro Porta/Miami Herald Tribune/New service via Getty

# Stiamo assistendo all'obsolescenza delle malattie infettive (per come sinora le abbiamo intese)

Grazie alle migliorate condizioni di vita, alla applicazione delle norme igieniche, alle vaccinazioni, molte infezioni gravi del passato non sono più un pericolo. La quota residua di infezioni l'abbiamo curata bene con gli antibiotici, ma li abbiamo usati troppo diffusamente/siamo diventati troppo numerosi/troppo vecchi/troppo malati/sempre più abili nel trattare le malattie non infettive, dimenticando che proprio vincendo quelle infettive siamo diventati "passabilmente sani"* così da poter raggiungere un'età prima insperata

*Silvia Bencivelli "Eroica, folle e visionaria-Storie di medicina spericolata", Bollati Boringhieri 2023

Abbiamo usato gli antibiotici, approfittando della facilità del loro utilizzo, su tutte le creature viventi: uomini, animali e piante.

I batteri se ne sono accorti.

E si sono organizzati.

Adesso, molte delle malattie infettive che si manifestano, specie nei luoghi di cura, sono sostenute da batteri resistenti agli antibiotici.
Più che dalla patologia in sé, il pericolo viene dalla mancanza di una cura efficace, fenomeno che sappiamo  come sia destinato ad aumentare*.
Quello che non avevamo considerato è che l'altra piaga dei nostri tempi, il riscaldamento del pianeta in cui viviamo, potesse contribuire vivacemente all'aumento della antimicrobico -resistenza

*O'Neill, 2014

**Nature, 08 January 2024**

# Antibiotic resistance is a growing threat — is climate change making it worse?

**Researchers are studying how extreme weather and rising temperatures can encourage the spread of drug-resistant infections.**

By Carissa Wong

Flooding in Bangladesh in 2020 compromised the safety of water supplies.
Credit: Zabed Hasnain Chowdhury/SOPA Images/LightRocket via Getty


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Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe – A 30 country observational study
Hani E.J. Kaba [a], Ellen Kuhlmann [b], Simone Scheithauer [a]
Editorial
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and climate change is that of infections, particularly antibiotic-resistant infections.
the aspects of climate change that have already, will, and could possibly impact the prolifer
dissemination of antibiotic resistance are discussed.

# Association between antibiotic resistance and increasing ambient temperature in China: an ecological study with nationwide panel data

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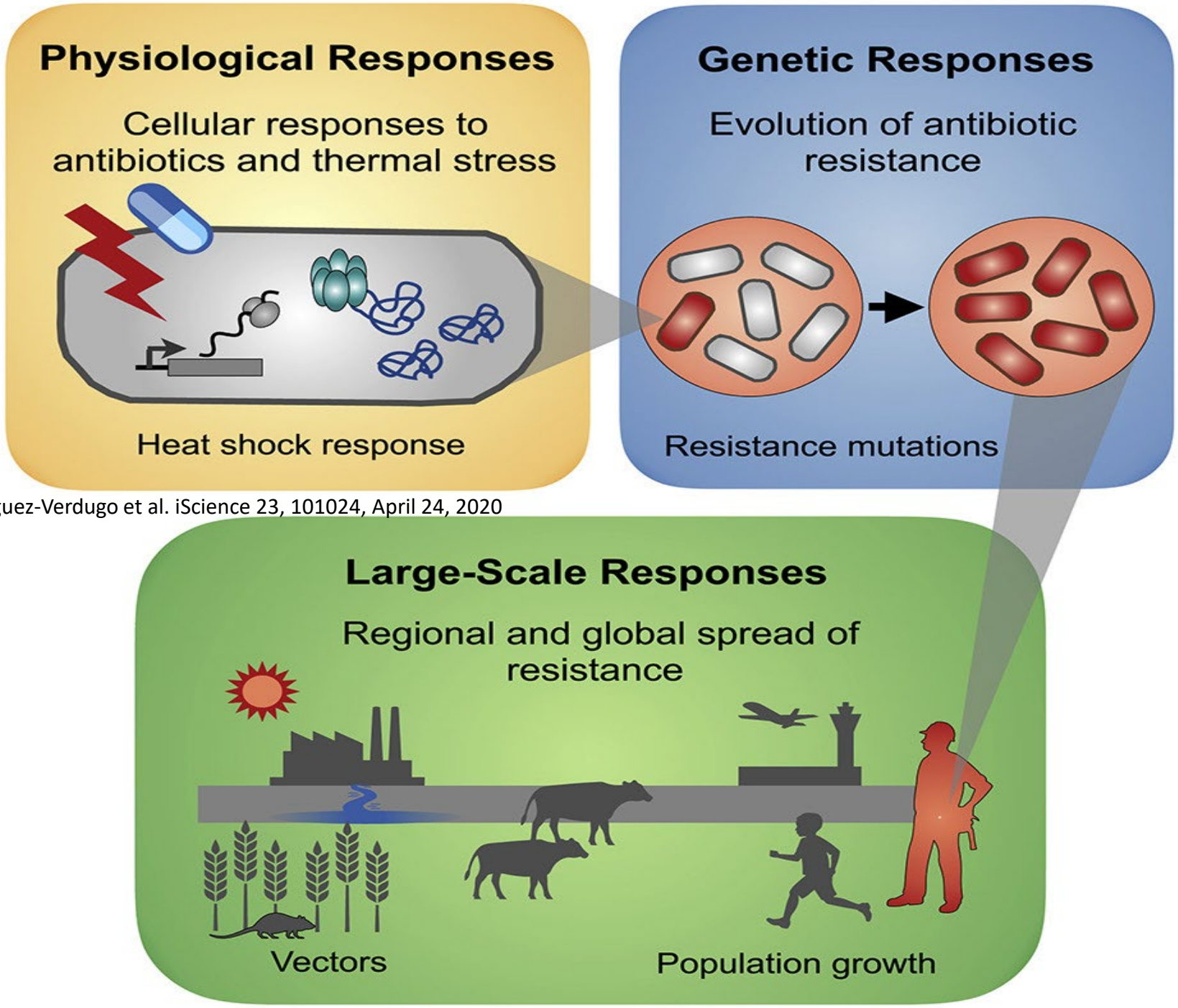
## Summary

**Background** Antibiotic resistance leads to longer hospital stays, higher medical costs, and increased mortality. However, research into the relationship between climate change and antibiotic resistance remains inconclusive. This study aims to address the gap in the literature by exploring the association of antibiotic resistance with regional ambient temperature and its changes over time.

**Methods** Data were obtained from the China Antimicrobial Surveillance Network (CHINET), monitoring the prevalence of carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Klebsiella pneumoniae* (CRKP) and *Pseudomonas aeruginosa* (CRPA) in 28 provinces/regions over the period from 2005 to 2019. Log-linear regression models were established to determine the association between ambient temperature and antibiotic resistance after adjustment for variations in socioeconomic, health service, and environmental factors.

**Findings** A 1 °C increase in average ambient temperature was associated with 1.14-fold increase (95%-*CI* [1.07–1.23]) in CRKP prevalence and 1.06-fold increase (95%-*CI* [1.03–1.08]) in CRPA prevalence. There was an accumulative effect of year-by-year changes in ambient temperature, with the four-year sum showing the greatest effect on antibiotic resistance. Higher prevalence of antibiotic resistance was also associated with higher antibiotic consumption, lower density of health facilities, higher density of hospital beds and higher level of corruption.

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## The Heat- and Cold Shock Stress Responses

The heat shock response then induces increased expression of two main sets of proteins: (1) **chaperones** to prevent and reverse the aggregation of misfolded proteins and (2**) proteases** to degrade misfolded protein aggregates. Besides protein misfolding, heat stress also causes increased membrane fluidity and damage to DNA and RNA. In addition to chaperones, a genomewide screen for genes essential for growth at high temperature (47C) in Escherichia coli found genes involved in **energy metabolism, outer membrane stabilization, membrane transport, DNA repair, tRNA modification, translation control, and cell division**.

In E. coli the main regulator of the heat shock response is the **sigma factor s32**, transcribed by the rpoH gene. High heat increases the concentration of free intracellular s32. In turn, s32 binds to the RNA polymerase and initiates the transcription of heat shock genes such as numerous global transcriptional regulators and genes involved in maintaining membrane functionality and homeostasis

Many chaperones, including DnaK, have been shown to participate in the negative regulation of the heat shock response by binding s32 and preventing it from activating the expression of heat shock genes.

DnaK also binds to unfolded proteins. As such, many other stresses that cause protein unfolding can compete for DnaK, freeing s32 and activating the heat shock response. Other organisms have different mechanisms to regulate the heat shock response, but its involvement in other stresses—especially those that cause protein misfolding—seems to be a common theme.

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## The Heat- and Cold Shock Stress Responses 2

The cold shock response has not been as extensively studied as the heat shock response and seems to be less conserved across organisms. **Under cold stress, DNA and RNA secondary structures are overstabilized**. This leads to a reduced efficiency of transcription and translation due to impaired movement of DNA polymerase and the ribosome, respectively. For instance, exposure of E. coli to cold initially stops growth and severely inhibits the synthesis of proteins except those that constitute the cold shock response. These cold shock proteins mitigate the damaging physiological effects of low temperatures, which include translational block, reduced membrane fluidity, slow protein folding, and increased negative DNA supercoiling. The cold shock response also modifies the metabolism of the cell to produce the sugar trehalose, which has a protective effect at low temperatures. Importantly, cold shock proteins have been shown to be involved in responding to various stresses besides low temperature such as oxidative stress, osmotic shock, acid stress, and ethanol.

## Similarity between the Physiological Effects of Antibiotics and Temperature

For example, **aminoglycosides** are a class of antibiotics that induce physiological effects in the cell that are qualitatively similar to those of **heat stress**. Aminoglycosides harm the cell through two main mechanisms:

(1) they bind to the ribosome and introduce errors in protein translation, producing aggregates of misfolded proteins, and

(2) they inhibit protein synthesis

Given that aminoglycosides increase misfolded proteins in cells, they also induce the heat shock machinery.

Indeed, DnaK and GroEL, chaperones involved in the heat shock response, have been shown to be induced in response to streptomycin in A. baumannii and E. coli. Overexpression of both the DnaK/DnaJ/GrpE and GroEL/GroES chaperone systems have a protective effect against sublethal concentrations of gentamicin.

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Although aminoglycosides provide a compelling example, similarity to temperature-induced damage is by no means an exclusive feature of this antibiotic class. In a study exploring the effects of several antibiotics that bind to the ribosome **in E. coli**, it was observed that the protein expression profiles of bacteria exposed to **many non-aminoglycoside protein synthesis inhibitors (macrolides, fusidic acid, and tetracycline)** is similar to that induced under **cold shock** (VanBogelen and Neidhardt, 1990). Another line of evidence supporting the similarity between physiological effects caused by antibiotics and temperature stress comes from genetic manipulations in **Staphylococcus aureus**. Notably, **deletion of cspB—a** major cold shock gene—was found to modify antibiotic susceptibility. Specifically, it **resulted in increased resistance to aminoglycosides** (~80-fold for gentamicin) **and trimethoprim** (>16-fold) as well as **increased sensitivity to daptomycin** (~20-fold) **and teicoplanin** (~4-fold), as measured by changes in the minimum inhibitory concentration (MIC; Duval et al., 2010).

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**Antibiotic Classes with Similar Physiological Effects to Heat.**

Aminoglycosides—gentamicin, tobramycin, and streptomycin—were found to interact similarly in E. coli to 46C, the highest temperature evaluated in Cruz-Loya et al. (2019). The protein-expression profile induced by kanamycin, streptomycin, and puromycin in E. coli has also been found to be similar to that induced under heat shock.
**These observations are likely due to the similarity between the effects of temperature-induced protein unfolding and aminoglycoside-induced misfolded proteins due to translational misreading .**
The presence of misfolded proteins under aminoglycosides may induce the expression of chaperones involved the heat shock response, as has been shown for DnaK and GroEL in A. baumannii (Goltermann et al., 2013). Overexpression of the heat shock chaperones DnaK and GroEL has also been shown to confer protection against sublethal concentrations of gentamicin in E. coli (Goltermann et al., 2013).

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| Antibiotic Class: Antibiotic Tested (Abbreviation) | Cellular Process (Effect) | Protein Expression Similarity | Interaction Similarity |
|---|---|---|---|
| Chloramphenicol: | Protein synthesis (inhibition) | Cold shock | Not measured |
| Chloramphenicol (CHL) | | | |
| Macrolides: | Protein synthesis (inhibition) | Cold shock (SPR, ERY) | Cold (22°C–25°C) (ERY, CLI) |
| Clindamycin (CLI) | | | |
| Erythromycin (ERY) | | | |
| Spiramycin (SPR) | | | |
| Fusidanes: | Protein synthesis (inhibition) | Cold shock | Not measured |
| Fusidic acid (FUS) | | | |
| Tetracyclines: | Protein synthesis (inhibition) | Cold shock | Cold (22°C–37°C) |
| Tetracycline (TET) | | | |
| Fluoroquinolones: | DNA supercoiling | Not measured | Cold (22°C–37°C) |
| Ciprofloxacin (CPR) | | | |
| Levofloxacin (LVX) | | | |
| Folic acid synthesis inhibitors: | DNA synthesis (Reduction) | Not measured | Hot (44°C) |
| Trimethoprim (TMP) | | | |
| Nitrofurans: | Multiple, including damage to DNA | Not measured | Hot (44°C) |
| Nitrofurantoin (NTR) | | | |
| Aminoglycosides: | Protein synthesis (misfolding and aggregation) | Heat shock (KAN, STR, PUR) | Very hot (46°C) (GEN, TOB, STR) |
| Gentamicin (GEN) | | | |
| Kanamycin (KAN) | | | |
| Puromycin (PUR) | | | |
| Streptomycin (STR) | | | |
| Tobramycin (TOB) | | | |
| Beta-lactams: | Cell wall synthesis | Not measured | None |
| Ampicillin (AMP) | | | |
| Cefoxitin (FOX) | | | |

## Sequential Exposure to Antibiotics and Temperature

La sopravvivenza di molti microrganismi ad uno stress aumenta di circa 10 volte dopo un'esposizione ad un altro tipo di stress.

La cross-tolleranza agli stress sarebbe più forte quando il danno indotto è simile: il primo stress "prepara" al secondo.

Temperatura e aminoglicosidi appaiono intercambiabili in queste azioni

## Persister Cells

Le cellule persistenti possono comparire casualmente, in una popolazione batterica, o essere indotte da uno stress, e rimanere tali anche a stress cessato.

## Genetic Adaptations to Temperature and Antibiotic Stressors
## De Novo Evolution of Antibiotic Resistance

Gli effetti indicati sinora sono transitori, ma la temperatura può avere effetto anche su caratteri ereditabili verificatisi per mutazione genetica, che porta alla evoluzione della antibiotico resistenza.

Questa può avvenire per mutazione spontanea o essere acquisita per trasferimento orizzontale (più comune a 30°C che a 25°C in E.coli, Walsh et al. 2011)

Mutazioni capaci di conferire resistenza allo stress da temperatura possono dare resistenza ad antibiotici e viceversa (resistenza collaterale).

E. coli esposto a 42°C per 2000 generazioni, in un esperimento sull'evoluzione, generò circa il 10% di linee con mutazioni de novo per resistenza a rifampicina, senza esservi mai stato esposto. Il target molecolare è lo stesso, la RNA polimerasi*.

Altro meccanismo per acquisizione indiretta di resistenza è la transizione a un diverso stile di vita (biofilm, per esempio).

Altro meccanismo è l'aumento di mutazioni spontanee: aumentata mutagenesi durante la risposta heat shock e stress response in generale (errori DNA pol, down regolazione della correzione degli errori)

*Rodriguez-Verdugo et al., 2016

Quando compare una mutazione, si fissa o viene persa, in base al vantaggio che offre. In presenza di antibiotico, il gene per la resistenza serve; in assenza, le mutazioni possono essere costose da mantenere. **Sembra però che le mutazioni di resistenza possano fare eccezione: varie resistenze alla rifampicina conferiscono vantaggio durante lo stress termico, in quanto l'espressione genica tornerebbe ad uno stato "non stressato", per le mutazioni in rpoB che risultano vantaggiose a 42°C***.

*Rodriguez-Verdugo et al., 2016