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THEMATIC COLLECTION: STANDARDS & THEIR CONTAINERS

ORIGINAL RESEARCH ARTICLE

Northern Normal: Laboratory Networks, Microbial Culture Collections, and Taxonomies of Power (1939–2000)

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Abstract

Bacteriophage-typing – using bacterial viruses to identify bacteria at the species and strain level – was the gold standard technology underlying the rapid expansion of international surveillance for major bacterial pathogens after 1945. The microbiological networks, taxonomies, and culture collections produced by phage-typers underpinned important advances in scientists' understanding of microbial diversity and infection control efforts. However, embedded geopolitics, extractive microbial sampling, and cultural biases also distorted typing efforts and resulting findings in favour of high-income countries. Northern Normal merges classic historical research on phage-typing archives and publications with spatial analysis using ArcGIS to reconstruct the origins, rise, and biases of international phage-typing. Focusing on typing efforts for Salmonella enterica serovar Typhi (the cause of typhoid fever), it shows how (post)colonial phage-typing networks cemented the dominance of Northern microbiological hubs and led to an inverse reading of microbial prevalence and relevance. Whereas strains prevalent in the Global North were designated universal, those from endemic areas in the South were exoticized. The article tracks how taxonomic distinctions between 'universal' Northern strains and high-prevalence 'exotic' strains reinforced biosecurity concerns about the reimport of typhoid from Southern countries, led to the choice of nonrepresentative strains to test typhoid vaccines, and facilitated growing neglect of typhoid at the international level. The article ends by reflecting on the persistence of (post)colonial microbiological infrastructures and resulting surveillance distortions in the genomic era.

Keywords

bacteriophages; typhoid; typing; taxonomy; microbiology

Introduction

Microbial pathogens are neither timeless nor static. Hiding beneath seemingly simple disease labels like typhoid, cholera, or plague are a multitude of constantly evolving bacteria strains with a range of virulence and resistance factors that can be exchanged with other bacteria. The overall make-up of a bacterial species

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and the long-term survival of individual strains is affected not only by interbacterial competition, but also by human actions. Over time, human migration, environmental change, and antimicrobial use have all impacted microbial diversity and prevalence.

Knowledge of the vast diversity of the microbial world increased substantially in the 20th century and underpinned advances in public health and disease surveillance (<u>Hardy 2015</u>; <u>Wall 2013</u>). Early identification ('typing') technologies which allowed researchers to differentiate between individual bacteria strains below the species level emerged from around 1900 onwards (<u>Kirchhelle 2019</u>; <u>Podolsky 2006</u>). However, access to this knowledge and the means to produce it spread unevenly. Due to their expense, typing capabilities often remained limited to well-funded research hubs in the Global North (<u>Velmet 2020</u>; <u>Chakrabarti 2012</u>). Geopolitics also influenced the ability to conduct microbiological research. Even when they had access to state-of-the-art typing technologies, workers in Southern laboratories often found themselves constrained by laboratory protocols and taxonomies, which were ill-suited to study local microbiomes and lack of representation on the international research bodies establishing these norms.

Northern Normal lifts the lid on the norms and 'hidden infrastructures' (Bowker and Star 2000) underpinning global disease surveillance and typing efforts. Building on the now substantial body of social sciences and humanities scholarship on infrastructures, it shows how the international spread of microbiological infrastructures not only enabled the movement of microbial matter, but also reflected contemporary power asymmetries. Carefully controlled infrastructural growth mirrored and reinforced wealthier Northern – often imperial – states' attempts to maintain control over samples and knowledge production during a time of increasing interest in microbial industries and concerns about microbial vulnerability. While every infrastructure inevitably remains patchy, the highly uneven evolution of international surveillance capacities and resulting microbial knowledge was thus less a result of Southern constraints than of Northern biopolitics.

The article traces these biopolitical trajectories by engaging in detailed historical reconstruction of the emergence of the first international microbiological surveillance network for typhoid. Caused by Salmonella enterica serovar Typhi, typhoid fever is an enteric disease with symptoms ranging from fever to diarrhoea and constipation. If untreated, typhoid kills up to one in five of people infected with it and continues to be responsible for millions of cases of sickness and between 118,000–271,000 deaths per year - with the highest mortality occurring in children in low-income settings (Ikuta et al. 2022). Although serological tests for typhoid date back to 1896, systematised attempts to study not just overall typhoid incidence, but also microbial diversity within S. Typhi started in the interwar period and were closely associated with the spread of a revolutionary new surveillance technology called bacteriophage-typing. Originating in Weimar Germany (Kirchhelle 2019), phage-typing uses standardised sets of bacteriainfecting viruses (bacteriophages) to differentiate between bacterial strains. Its' ease of use, fine-grained resolution, and biological characteristics allowed phage-typing to rapidly outcompete other contemporary serological and biochemical typing systems. Despite being displaced by molecular typing methods from the 1990s onwards, phage-based taxonomies and infrastructures including sampling networks and microbial culture collections continue to impact biomedical research such as the choice of strains used to test vaccines or inform phylogenetic studies.

Focusing on the international spread and institutionalisation of phage-typing for typhoid between 1938 and 1980, the article argues that paying attention to the historical genesis and biases of resulting

phage-based collections, taxonomies, and sampling networks is important for both humanities and biomedical researchers. While global phage-typing produced important new 'viral' ways of understanding typhoid diversity and invaluable archives of past microbial environments, (post-)colonial sampling networks, what we now term biosecurity politics,¹ and cultural biases systematically distorted resulting taxonomies, networks, and collections. Similar to other technical infrastructures (<u>Star and Ruhleder 1996</u>), the substantial scientific work, trade-offs, and political struggles that were involved in the phage-based ordering of Salmonella enterica serovar Typhi (the bacterial cause of typhoid fever) remained invisible to most of the clinicians, officials, and researchers who used resulting microbiological standards to design and test vaccines, organise epidemiological surveillance, and roll out treatments and diagnostics.

Unsurprisingly, infrastructural opacity served some interests more than others. Foreshadowing problems of current preparedness strategies (<u>Lakoff 2017</u>), phage-based surveillance data helped perpetuate the (post)colonial biases of the primarily European and North American sampling networks it was produced by. Focusing on controlling so-called exotic strains, surveillance was most intensive in low-prevalence areas in Europe and North America while decision-makers displayed little interest in capacity building beyond limited microbial sampling in Africa, Asia, and South America. Surveillance gaps in turn distorted assumptions about microbial prevalence and relevance and helped justify national biosecurity regimes that focused on controlling typhoid at high-income borders rather than in endemic high-prevalence areas.

The first part of the article focuses on the period between 1938 and 1947 and shows how phagetyping's rapid rise rested on its' microbiological specificity, stability, and ability to process significant numbers of microbial samples in a uniform way, as well as facilitation of bacteriological centralisation. By the 1950s, what had started as an informal network of researchers employing a still poorly understood set of viruses to gain bacterial type information had transformed into the gold standard for studying global microbial diversity.

The second part of this article builds on Joanna Radin's (<u>Radin 2017</u>) and Jenny Bangham's (<u>Bangham 2014</u>) work on 20th century blood surveys and biobanks to study the 'embedded' politics of the global phage-typing infrastructure. Similar to Michael Bresalier's pioneering work on the Global Influenza Programme (<u>Bresalier 2023</u>) and other examples of post-war 'internationalism' (<u>Manton and Gorsky 2018</u>), a quantitative and geographic evaluation of data published by the International Committee of Enteric Phage Typing (ICEPT) shows that the means for phage-based microbial processing were unevenly distributed. In a repeat of a familiar story, most Southern laboratories ended up exporting typhoid samples to Northern centres with little return investment in local laboratories. This logic suited the biosecurity and geopolitics of Northern hubs, who maintained firm control over the means of microbial data processing and sampling. In contrast to other phenotypic surveillance programmes' reliance on reagents that could also be produced

¹ According to the Oxford English Dictionary (<u>www.oed.com</u>, accessed December 12, 2023), the term biosecurity was only coined in 1973.

locally (<u>Bresalier 2023</u>), Northern control was further consolidated by phage-typing's dependence on the global mass distribution of an authoritative viral typing set that could only be produced in one location.

Part three uses ArcGIS to visualise the rather dry tabular data from ICEPT surveys. It shows how the (post-)colonial dynamics of microbial sampling and processing became embedded in international taxonomies. Similar to the 'molecular politics' (Crane 2011) of HIV research, ICEPT's phage sets and taxonomies produced an authoritative yet inverse reading of the world: higher sampling in wealthy areas with low typhoid incidence and the biological origins of typing phages in Northern environments meant that European and North American typhoid strains were considered 'universal', 'cosmopolitan', or 'ubiquitous'. By contrast, taxonomies labelled Southern strains 'regional' or 'exotic' – despite far higher overall prevalence. This almost classically Foucauldian use of inherently biased biostatistics to 'normalise' Northern typhoid ecologies seemed to justify harsher forms of control and governance for so-called exotic strains and carriers in areas where they were deemed 'abnormal'. It also created an international surveillance regime that focused on border controls and spot surveys rather than growing diagnostic infrastructures in high-prevalence areas. Part four of the article ends by reflecting on the manifold consequences and continuities of (post-colonial) microbial sampling networks and systemically distorted collections and phage-based taxonomies in the genomic age.

Part One: Origins (1938-1947)

Sometime in 1938, a parcel containing vials of transparent fluid was delivered to the British Ministry of Health's small Endell Street Laboratory in London. The parcel had been posted from Toronto and was addressed to renowned typhoid expert William MacDonald Scott (<u>WL 1</u>). Contained in the eleven vials were bacteriophages – ultramicroscopic viruses that infect bacteria and either rapidly destroy them (*lytic phages*) or embed themselves in the bacterial genome (*lysogenic phages*). The phages' arrival in London heralded the birth of a transformative international network for bacteriological surveillance.

Since the 1920s, researchers had tried to harness the specificity with which bacteriophages attack bacteria to identify – type – microbes at the species and strain level. In Weimar Germany, researchers initially used phages to speed up typhoid and paratyphoid diagnosis and then began to use sets of standardised typing phages to differentiate between different strains of a bacterial species. Typing phages were isolated from the circular lytic plaques – clearings – they created on lawns of their bacterial hosts on petri dishes. Once isolated, phages could easily be propagated by reinfecting the bacterial cultures they were supposed to lyse (destroy) and harvesting phages from plaques. Despite contemporary uncertainty about their viral or enzymatic 'nature', phages reliably revealed phenotypic (observable) differences amongst bacterial strains that could not be picked up with serological (antigen-antibody reactions) or biochemical methods (<u>Anderson and Williams 1956; Kirchhelle 2019</u>).

In 1934, the discovery of the virulence associated polysaccharide (Vi-antigen) of the typhoid bacterium S. Typhi by Arthur Felix and Margaret Pitt at London's Lister Institute triggered a rapid expansion of phage-typing research. Although not all typhoid strains express it, an outer capsule of Vi-polysaccharides helps S. Typhi bacteria evade the body's immune response by preventing innate immune recognition via complement (<u>Wilson et al. 2011</u>). This 'cloaking device' means that Vi-positive organisms have a significantly higher virulence rate, which makes them of key public health interest (<u>Wain et al. 2005</u>). By developing new phage-based diagnostics targeting the Vi-polysaccharide, researchers hoped to speed up

routine laboratory diagnosis of typhoid infections, differentiate between virulent and non-virulent strains, and trace the source of typhoid outbreaks with similar phage-profiles (<u>Kirchhelle 2019</u>).

A team led by Scottish microbiologist James Craigie at Toronto's Connaught Laboratories was the first to crack this challenge. In 1936, Craigie's team had isolated Vi-specific phages from bacterial cultures obtained from the faeces of typhoid patients (Craigie and Brandon 1936). After first using their phages to study virus-host relationships (WL 12), they became interested in epidemiological applications. Together with his Chinese colleague and Rockefeller Foundation grantee, Chun Hui Yen (RAC 1), Craigie tested the typing potential of four serologically distinct Vi-phages by analysing their selective action on preserved and fresh S. Typhi isolates from distinct Canadian, Chinese, Scandinavian, and British outbreaks (Anderson and Williams 1956). However, rather than differentiating between these isolates, phages I, III, and IV lysed (destroyed) the majority of them, which made the three phages unsuitable for epidemiological research. Fortunately, phage II had 'a high selective lytic activity for the type of B. typhosus on which it is propagated' (Craigie and Yen 1938a). This meant that a process of infecting a distinct S. Typhi strain with phage II, harvesting descendants of the phage from lysed bacterial cells, and using these harvested phages to infect new cultures of the same distinct S. Typhi strain (a process known as passaging) would eventually make descendants of the original phage only attack the S. Typhi strain they had been repeatedly passaged on. Craigie and Yen surmised that phage II's selective activity was due to mutations, which occurred after it infected a bacterial host - and that the phage mutations indicated biological differences within the S. Typhi species (<u>Figure 1</u>).

This was a doubly significant finding. On the one hand, the discovery of distinct typhoid phage types contradicted popular assumptions of the 'typhoid bacillus [...] as one and indivisible [...], and indeed in that sense an oasis of simplicity in the desert of complexity which constitutes the remainder of the enteric group...' (BMJ 1938).² On the other hand, the type specificity of the phage II mutants opened the door for a new Vi-phage-based epidemiology. By propagating their original Type II phage on large numbers of bacterial typhoid isolates, Craigie and Yen could simultaneously identify distinct *S*. Typhi types and produce highly specific mutated typing phages with which to reliably reidentify the *S*. Typhi type they had been passaged on (Craigie and Yen 1938a). Between 1936 and 1938, Craigie and Yen infected hundreds of *S*. Typhi isolates with their phage II until they had established a set of phage II mutants that identified 11 *S*. Typhi types via lysis (Nicolle 1964; Craigie and Yen 1938a; Boyd 1939) and reliably assigned the same phage type to epidemiologically related samples (Craigie and Yen 1938b).

² Researchers were already aware of virulence variations between *S*. Typhi strains and had also observed phenotypic variations induced by phages and prolonged culturing but most continued to consider *S*. Typhi as one organism rather than a species consisting of multiple distinct types (<u>Nicolle 1964, 71; Kirchhelle 2019</u>).

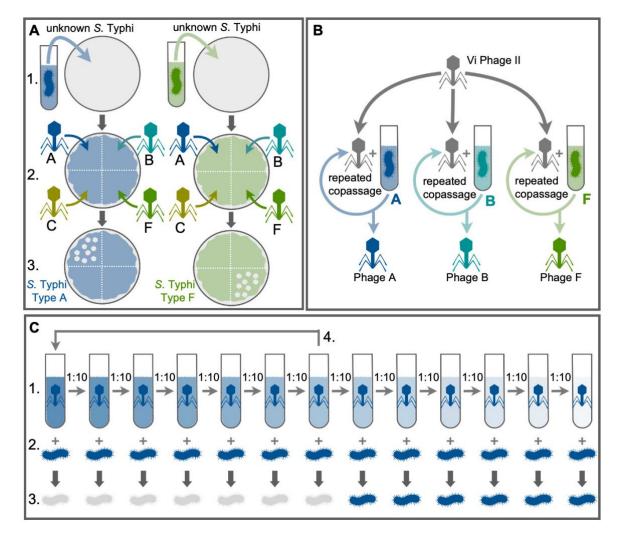


Figure 1. Principles of Vi-phage typing for *S*. Typhi and Vi phage adaptation (Source Authors' Own). **Legend:** (A) *S*. Typhi phage typing procedure.:1. Cultures of unknown *S*. Typhi strains are plated on solidified growth medium and inoculated to stimulate uniform growth. 2. A set of type-specific phage are added to the seeded plate. 3. After further inoculation, plates are scored for phage-induced lysis (clear plaques in the bacterial lawn). The type of the bacterial culture corresponds to the phage type it is sensitive to. (B) Repeated co-passaging of Type II Vi phage with different strains (A,B, . . . ,F) of *S*. Typhi produces phages specific to the respective host strain. (C) Co-passaging procedure: 1. Type II Vi phage culture is diluted in a 10-fold dilution series (up to 1012). 2. Diluted phage cultures are mixed with cultures of the host strain at the same concentration. 3. The culture is incubated over night and examined for bacterial growth (blue) or lysis (grey). 4. The highest dilution of phage resulting in complete lysis of the bacteria is selected and used for the next round of co-passaging (starting with step 1.)

The Canadian team next asked foreign laboratories to trial their technique. Winning endorsements from international experts was crucial if use of Craigie and Yen's typing phages was to spread beyond Canada. The chances for this were good: alternative phage-typing systems were still experimental and competing biochemical and antibody-antigen typing schemes for typhoid were slower, more expensive, and less precise (<u>Kirchhelle 2019</u>). One of the researchers they contacted was William Scott of London's Ministry of

Health laboratory. Although Scott did not 'have the time or the inclination to work with' the package containing Craigie and Yen's phages (TNA 1), he passed it on to his friend, John Smith Knox Boyd of the Royal Army Medical Corps (RAMC). Boyd was a senior military bacteriologist who had trained under bacteriophage co-discoverer Frederick Twort during World War One. During the interwar period, Boyd had spent extensive time working on enteric infections in India and had only recently returned to Britain to head the Army's Vaccine Department at Millbank (Goodwin 1982). His time in India made Boyd appreciate the need for more fine-grained typhoid diagnostics as well as phages' therapeutic and epidemiological potential (Boyd 1939; TNA 1; Summers 1999).

Boyd's interest placed Craigie and Yen's phages at the heart of one of the most extensive typhoid sampling networks in the world and provided an ideal way to showcase their usefulness. Britain's military had conducted systematic serology and culture-based typhoid testing since World War One (<u>Boyd 1939</u>; <u>Bhatnagar 1938</u>; <u>Gradmann, Harrison, and Rasmussen 2019</u>). Between February and September 1939, Boyd tested Craigie and Yen's Vi-phages on numerous typhoid samples from military and civilian sources – the latter supplied by Scott – double-checked Canadian claims on archived samples, and unravelled complicated ongoing outbreaks (<u>Boyd 1939</u>; <u>WL 2</u>, <u>WL 4</u>, <u>WL 6</u>, <u>WL 7</u>, <u>WL 8</u>, <u>WL 9</u>). The imminent outbreak of World War Two interrupted his studies. After giving two presentations on phage-typing at the 1939 meetings of the Royal Society for Tropical Medicine (RSTM) and the British Medical Association (BMA), Boyd was sent to North Africa where he would continue to use Craigie and Yen's phages to study enteric fever but no longer played a central role in the technology's development (<u>WL 1</u>).

Boyd's departure came at a crucial time for British bacteriology. Concerned about biological warfare and epidemics, the government had laid plans for a centralised wartime Emergency Public Health Laboratory Service (EPHLS) to run laboratories across England and Wales (<u>Williams 1985; Kirchhelle 2022</u>). The EPHLS was officially mobilised on 25th August 1939 and workers took up their posts at 25 laboratories across the country (<u>WL 16</u>). What happened next was unexpected in that nothing happened. The absence of significant enemy action during the 'phoney war' between September 1939 and the first large-scale Luftwaffe attacks in September 1940 meant that EPHLS workers had comparatively little to do (<u>Wilson</u> 1948b, 1948a; <u>TNA 2</u>).³ With time and a growing number of bacteriological samples on their hands, they engaged in war-related research (<u>Williams 1985; TNA 4, TNA 13</u>).

At Oxford's Dunn School for Pathology, EPHLS bacteriologist Arthur Felix turned his attention to perfecting Craigie and Yen's phage-typing system. As the co-discoverer of the O-, H-, and Vi-antigens, Felix was a world-authority on enteric organisms. Although he was well-acquainted with Craigie's work (<u>Craigie 1957</u>),⁴ it had been Boyd who had introduced Felix to phage-typing. At the 1939 RSTM meeting in London, Boyd had noted that Felix was in attendance and 'greatly intrigued by the demonstration' whilst taking 'exhaustive notes' (<u>RAC 1; Goodwin 1982</u>). Felix' fascination with Craigie's phage-typing system was heightened by the discovery that some of the allegedly identical strains in his own collection belonged to

³ See the war diary kept by EPHLS lab assistant Sidney Chave (TNA 14).

⁴ Another major wartime project of Felix was to upgrade the British Army's typhoid and paratyphoid A and B (TAB) vaccine with a new alcohol killed and preserved revived Rawlings strain (<u>Craigie 1957; TNA 12</u>).

multiple *S*. Typhi phage types and had either been contaminated or undergone type changes while in storage (<u>Craigie 1957</u>).

After receiving his own phage set from Craigie (<u>ibid.</u>), Felix began to use and adapt it to link and trace typhoid outbreaks and map disease prevalence across Britain. In July 1940, an EPHLS memorandum asked for all S. Typhi isolates to be forwarded to Felix so 'that the distribution of the various phage types throughout the country may be determined, and the value of this method for tracing epidemic spread more fully investigated' (<u>TNA 3</u>). With Boyd stationed in North Africa, Yen working at Peking Union Medical College,⁵ and Craigie focusing on Allied typhus research (<u>WL 11, WL 12</u>), it was Felix who would establish phage-typing as the new international gold standard for typhoid identification.

It did not take long for impressive results to emerge. Although security concerns led to heated debates about which investigations could be published (TNA 15, TNA 16, TNA 17), the first issue of the *EPHLS Monthly Bulletin* from November 1941 reported that phage-typing had enabled Felix to identify asymptomatic carriers, discover new S. Typhi phage types, and provide valuable support for clinical trials of sulfonamides to treat typhoid carriers (TNA 7, Felix 1941). Numerous reports followed on Felix' development of typing systems for other salmonella species and the use of Vi phage-typing to solve typhoid outbreaks amongst British civilians and the Allied forces (TNA 8, TNA 9).

By 1941, phage-typing was thus rapidly establishing itself as a new system for typhoid surveillance. Its success was based both on the remarkable adaptability of the Vi II phage and on skillful networking by Craigie. While the first era of phage-typing was dominated by personal networks between key researchers, its second era would be shaped by the politics of the large networks supplying typers and their bacterial viruses with microbial samples.

Part Two: A Flood of Data

The wartime centralisation of Britain's bacteriological facilities provided phage-typing with a microbial infrastructure in which it could thrive. Between September and December 1939, the EPHLS examined between 2,000 and 3,000 microbial samples (i.e. <u>TNA 4</u>, <u>TNA5</u>). By 1947, the annual number of samples had risen to 468,000 (<u>Williams 1985</u>).

As a technology, phage-typing was ideally suited to processing this flood of biological material. Between 1942 and 1949, Felix used Craigie and Yen's phages to type 2,892 typhoid cultures from 1,834 individual cases. The result was a virtuous circle of data processing: the more typhoid samples Felix processed via phage-typing, the easier it was to argue for additional samples to be typed in the same way so that results could be compared and used in the field. Similar to contemporary internet search engines, whose success rests not on absolute control of data but on the ability to train and refine algorithms based on indexing and ranking content, phage-typing's true power thus rested in its ability to consolidate and control

⁵ Yen returned to Beijing in 1938 eager to assist Chinese nationals in view of the 1937 Japanese invasion; the Rockefeller funded Peiping Union Medical College soon granted him a position as Assistant Professor, where he isolated and defined two new phage types P15 and P16 in 1939 and tried to use Vi phage II to produce therapeutics (Yen 1939; Yen and Chang 1941; Yen and Chen 1940; RAC 1).

the means of data processing. This logic certainly held true in Britain. Whereas Felix had only received samples from ca. 36% of notified British typhoid cases in 1942, this quota had risen to 96% by 1949 (Felix 1951).

The growing stream of typhoid samples reaching Felix' laboratory led to a sharp increase in the number of known phage types and a decrease in the percentage of untypable strains (<u>TNA 5;-ibid.; Craigie</u> <u>and Felix 1947</u>). The original 1938 typing system had comprised 11 Vi-phage types. Further adaptations via passaging by Craigie and Felix increased this number to 24 by the end of the war (<u>Craigie 1946; Felix 1951</u>).⁶

In the face of new record lows of British typhoid mortality (<u>TNA 10</u>), Felix and his co-workers also began to move from merely controlling to eradicating endemic typhoid (<u>Felix 1951</u>). Key to this endeavour was combining centralised typing with epidemiological databases that could link seemingly disconnected typhoid cases. By methodically typing current and historical *S*. Typhi isolates from across Britain, Felix had begun to build a so-called fingerprint registry of known typhoid carriers and their phage types from ca. 1941 onwards. As can be seen in Figure 2, this registry could be used to respond to acute outbreaks and uncover historical transmission chains. In conjunction with new technologies such as sewage swabs, it could also be used to 'hunt' for hitherto unknown local typhoid carriers and identify the introduction of novel typhoid types (<u>Murdock and Lawson 1955</u>; <u>Anderson and Williams 1956</u>).⁷ By centralising bacterial processing and connecting type and epidemiological data, Felix had effectively moved typhoid epidemiology from an ad and post hoc mode of case-based investigations (<u>Steere-Williams 2020</u>) to a proactive system of surveillance and case control based on viral specificity.

⁶ Craigie continued to work on consolidating his system and expanding it to account for resistant types, which he suspected contained 'symbiotic' or 'cryptic' (i.e. lysogenic) viruses in 1941 (<u>WL 12</u>).

⁷ A Vi-register of all enteric fever patients and carriers was maintained after 1945 (<u>WL 17, WL 3</u>).

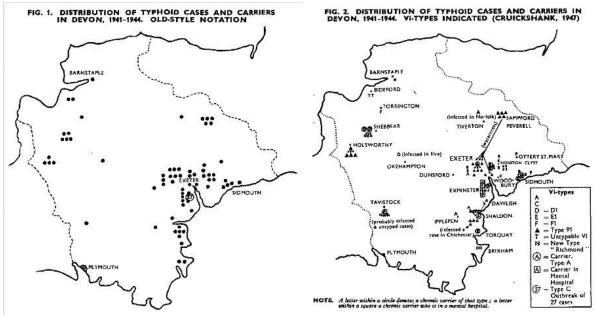


Figure 2. From case-based to type-based typhoid epidemiology (Source Felix 1951).

Legend. Typhoid control was transformed by phage-type data, which allowed public health workers and epidemiologists to differentiate between different strains of a pathogen. The left map from 1947 shows notified cases of typhoid in Devon, the right map from the same year shows transmission pathways based on phage-type assignation.

Ambitions for typhoid eradication were further boosted by the EPHLS' 1946 transformation into a peacetime Public Health Laboratory Service (PHLS). Headquartered in Colindale in North London, the PHLS continued to offer typing services for Medical Officers of Health and became an important partner for the new National Health Service (NHS), which was created in 1948. Between 1947 and 1953, the number of PHLS laboratories more than doubled from 28 to 60. Meanwhile, the annual number of samples processed by the PHLS network more than tripled from 468,000 specimens in 1947 to 1,786,000 in 1957 (<u>Williams 1985; Kirchhelle 2022</u>).

Increased knowledge of domestic typhoid ecologies fostered interest in foreign phage types. Underlying this interest was more than scientific curiosity. Instead, it was a prolongation of long-standing concerns about protecting Europe from often orientalised 'exotic' disease threats (Weindling 1995; Velmet 2020; Harrison 2012; Packard 2016). In the case of typhoid, improved knowledge of 'exotic' phage types was seen as key to protecting Britain against the importation of new strains. Created as a biodefense organisation, the EPHLS had already attempted to identify potential bacteriological sabotage involving enteric organisms during the war (TNA 6). By 1943, Arthur Felix had become convinced that only 13 typhoid types or subtypes were truly 'indigenous' (Felix 1951, 1943a) to Britain and that other types were nearly always introduced from abroad. In November 1944, an interdepartmental conference proposed establishing a phage-based fingerprint file for returning members of the armed forces – 2,000 of whom had contracted typhoid fever and 40 of whom were expected to become carriers (TNA 11). Public health authorities were also concerned about other forms of importation resulting from merchant seamen and, following the end of World War Two, migrants and tourists (Felix 1951; Craigie and Felix 1947). To progress from typhoid control

towards eradication, it was necessary to maintain rigorous screening of people entering Britain and gather more information about 'exotic' phage types.

British typers could not map the global diversity of *S*. Typhi by themselves. Similar to parallel UK efforts to build an international network of influenza surveillance (<u>Bresalier 2023</u>), such a project required international collaboration, sophisticated networks of microbial exchange, and centralised standard-setting. Felix and Craigie had discussed the need for an international system of phage-typing when Felix visited North America in 1945 (<u>Craigie 1957</u>). According to Craigie, quality concerns made them favour a formal organisation for phage-typing:

We both feared that the adaptability of typhoid II Vi phage, on which the typing scheme depended, could become the greatest menace to international exploitation of the method if inexperienced workers prepared their own supplies of typing phages from the reference strains supplied. Some, in so doing, had obtained preparations of modified specificity which their own limited tests failed to reveal. On one occasion this resulted in different type designations being allocated to strains from the same epidemic in two different states (<u>ibid</u>.).

The stability and ease with which large quantities of VI type II typing phages could be produced and the ability to store and distribute phages at 4C without further repassage made the task of creating an international system 'much simpler than [...] standardization of sera or agglutinable suspensions for serodiagnostic tests; matters in which Felix had had much experience [via Vi-testing]' (ibid.; WL 13). Reliance on centrally produced phages also made standardisation and control of resulting networks much easier than in the case of serological influenza surveillance (Bresalier 2023). According to Craigie, it was possible to 'prepare stocks [of individual typing phages] which would serve not merely as reference standards, but as actual working reagents for a considerable number of years' (Craigie 1957). Following Felix's visit, both researchers consolidated existing typing data into a new universal taxonomy of *S*. Typhi phage types. They also refined typing protocols and produced large batches of each typing phage, which would allow for more than 10⁸ (100 million) separate tests per batch (ibid.). Centralised phage production not only guaranteed comparable results, but also meant that interested laboratories could receive regular shipments of screw top vials of the most recent set of typing phages without having to maintain bacterial reference strains themselves.

Publication of Felix and Craigie's 'suggestions' for standardised phage-typing of typhoid bacilli in the Lancet (<u>Craigie and Felix 1947</u>) was shrewdly timed to coincide with the 4th International Congress of Microbiology in Copenhagen. Beginning in July 1947, the Copenhagen Congress was the first major gathering of microbiologists since World War Two. It assembled over 1,100 delegates from 35 countries and was divided into nine sections ranging from general to industrial microbiology (<u>Iohn-Brooks 1947</u>). The Congress was an important opportunity to re-establish microbiological networks that had been severed by the war. Occurring one year after the creation of UNESCO and one year ahead of the formal establishment of the World Health Organisation (WHO), it also provided an important forum to build on interwar microbiological standard setting and update taxonomic systems (<u>Weindling 1995</u>; <u>Mazumdar 2003</u>, 2010).

Felix was part of the more than 200-strong British delegation at the Copenhagen Congress and had arranged for a group of public health experts to discuss forming an international phage-typing network (<u>Craigie 1957</u>). The resulting International Committee for Enteric Phage Typing (ICEPT) was composed of

the directors of existing national and regional phage-typing laboratories. Felix served as the first director of ICEPT alongside Pierre Nicolle – son of famous Pasteurian Charles Nicolle (<u>Velmet 2020</u>; <u>Felix 1955</u>).

At the heart of ICEPT's mission was to 'secure international standardization of the routine phage typing of typhoid and paratyphoid bacilli as employed in epidemiological investigations directed to the control of the enteric fever' (<u>ibid., 112</u>). Building on Felix and Craigie's proposals, members agreed to use the same phages and typing protocols and engage in quality assurance via the exchange and testing of reference strains. New phage types identified by individual members would be validated by ICEPT (<u>Brandis 1957</u>; <u>Anderson 1962a</u>; <u>Nicolle 1962b</u>). ICEPT members would meet in parallel to the international microbiology congresses to update typing systems and taxonomies (<u>Felix 1955</u>).⁸

While international collaboration was necessary to generate a sufficiently geographically diverse number of microbial samples to map global type diversity, it was clear that very few laboratories had the expertise or technical capabilities to act as phage-typing hubs. The result was a clear hierarchy of ICEPT laboratories. Acknowledging the EPHLS' wartime achievements, ICEPT members designated Felix' Colindale laboratory as International Reference Laboratory for Enteric Phage-Typing. Colindale would maintain, propagate, and distribute the international reference set of initially 24 typing phages and corresponding *S*. Typhi reference strains. Felix' team could also be called upon to analyse select samples from other countries (<u>ibid.</u>), host and train aspiring foreign phage-typers, and develop laboratory networks in other countries – primarily in the Commonwealth (WL 15).

The resulting hierarchical flow of microbes, data, and methods within ICEPT suited British interests and guaranteed ongoing soft power over biomedical systems in other parts of the world during a time of rapid decolonisation.⁹ This (post-)colonial dimension of phage-typing should come as no surprise. Since the nineteenth century, international health meetings and organisations had often primarily served European and North American interests. While sophisticated public health infrastructures evolved in richer countries, health interventions in non-European contexts often centred on increasing the efficiency of indigenous workforces, protecting European settler populations, and stopping 'oriental' diseases from spreading to the 'West' (Harrison 2012; Packard 2016; Velmet 2020; Dublin in Weindling 1995; Manderson in Weindling 1995, 128–129). Despite renewed optimism about international disease control after 1945, the internationalist rhetoric of many health and scientific initiatives thus concealed substantial imperial continuities (Manton and Gorsky 2018; Bangham 2014; Crane 2011; Bresalier 2023; McVety 2018).

Enteric phage typing was no different. Although decolonisation meant that international collaboration could no longer be decreed, the phage-based surveillance infrastructures that were allowed to grow were grafted onto pre-existing mostly colonial networks and pruned to avoid lateral contacts with competing networks. Imperial powers like France and the Netherlands replicated the British model by maintaining control of microbial samples, expertise, and phage data flowing through their respective

⁸ Additional information on the way ICEPT and its successor organisation worked was gathered during a phone call with former IFEPT head, Linda Ward in 2020.

⁹ Colindale's reports to the WHO indicate a sustained stream of phage and typing requests from across the world as well as a large number of international visitors, who were trained in phage typing (<u>WHOA 3</u>).

(post-)colonial laboratory networks. Leading European typing centres were run by bacteriologists who had been educated in tropical medicine, had served or – in the case of Nicolle – grown up in imperial outposts, and believed in the 'civilising' mission of empire (<u>Velmet 2020, 1–18</u>; <u>Chakrabarti 2012</u>). Similar to interwar conflicts about international access to colonial data (<u>Dublin in Weindling 1995, 73–74</u>), major powers carefully controlled foreign access to their microbiological networks (<u>Lentzos 2016</u>; <u>Kirchhelle et al. 2024</u>). Cold War concerns about biological warfare also meant that knowledge of public health capabilities was an important intelligence asset. During the 1950s, America's Central Intelligence Agency (CIA) surveyed Soviet phage-typing infrastructure and vulnerabilities to biological attack (<u>GD 1</u>).While the US reported data on domestic phage types to ICEPT, neither superpower forwarded information on typhoid types isolated from foreign territories within their spheres of interest.

Driven by geostrategic interests, the geographic expansion of enteric phage-typing was rapid (See figures 3 and 4, Supplementary Table 1). ICEPT phages were quickly adopted throughout Western Europe and in select colonial and allied laboratories (Crocker 1947; Tolhurst, Buckle, and Hyams 1945).¹⁰ Paris in particular emerged as a major phage-typing hub. In 1940, Eugène Wollman had established a *Service des Bactériophages* at Institut Pasteur. Pierre Nicolle was placed in charge of the Service's laboratory in 1941 and assumed directorship after Wollman's deportation to Auschwitz in 1943 (Théodoridès 1985; Nicolle 1979). Following liberation, Nicolle began using Anglo-Canadian typing phages. Amidst declining post-war interest in phage therapy, epidemiological applications of bacteriophages gained importance (Dublanchet and Fruciano 2008; Turner et al. 2024). Nicolle was elected co-director of ICEPT alongside Felix and established an international 'lysotypie' service in 1948, which would go on to type more than 24,000 typhoid cultures between 1948 and 1974 (Théodoridès 1985).

	Africa	
South Africa	1941: University of Pretoria [C&Y phages; 1944–1947 AF phages; 1947 ICEPT phages] (<u>Crocker 1947</u>).	
Egypt	1939-1956: Central Pathology Laboratory, Fayid [phage typing for British Army Middle East Command [Egypt, Libya, Cyrenaica, Tripolitania, Malta, Cyprus, Syria, Palestine, Iraq, Iran, Sudan, and Eritrea via CY/ AF phages]. By 1973: US NAMRU-3 Cairo in collab. with Institut Pasteur [ICEPT phages] (ICEPT 1973 see <u>Anderson and Nicolle 1973</u>).	
Central Africa	1949-1960: Léopoldville's Centre d'Étude et de Diagnostic des Enterobactactéries pathogènes [ICEPT phages] in collaboration with Institut Pasteur (<u>Makulu in Gatti et al., 1968; Van Oye</u> and Nicolle 1953; <u>Reul 1949; Krubwa et al. 1970</u>).	
Oceania		

Supplementary Table 1.*

¹⁰ The RAMC Emergency Vaccine Laboratory at Everleigh also conducted phage-typing on 286 cultures from military personnel stationed in North West Europe, Italy, the Middle East, and West and North Africa; (<u>Wilson</u> <u>1947</u>).

Australia	1943: Alfred Hospital, Melbourne [AF phages] (<u>Tolhurst,</u> <u>Buckle, and Hyams 1945</u>).
	1947: Bacteriology Department [later Public Health Laboratory], University of Melbourne [ICEPT phages] (<u>Forsyth et al., 2003</u>).
New Zealand	By 1954: National Health Institute, and the Department of Pathology, Wellington Hospital, Wellington, New Zealand [ICEPT phages].
Ame	ricas
United States of America	1939: regional surveys in Colorado and Georgia [CY phages]
	1947: CDC enteric bacteriology unit, Atlanta [ICEPT phages] (Morris, Brim, and Sellers 1945; Henderson and Ferguson 1949; Lazarus 1940; Kendrick et al. 1951).
Brazil	1966: Oswaldo Cruz Institute, Rio de Janeiro [ICEPT] (ICEPT 1973, see <u>Anderson and Nicolle 1973</u>).
Canada	1938: Connaught Laboratories, University of Toronto [CY phages]
	1941: Bacteriophage Service, Division of Laboratories, Ministry of Health and Social Welfare of Quebec, Montreal [CY phages; from 1947 ICEPT phages] (<u>Desranleau 1947</u>).
Uruguay	1947-1950: Montevideo Institute of Hygiene [ICEPT phages] (<u>Felix 1955</u>).
Jamaica	1950: University of the West Indies, Mona Kingston [ICEPT phages] (<u>ibid.; Grant and Caselitz 1954</u>).
Eu	rope
Netherlands	1947: Rijks Instituut voor de Volksgezondheid, Utrecht [ICEPT phages] (<u>Scholtens 1950</u>).
West-Germany	1925-1946: German phage diagnosis and typing with Sonnenschein and Marcuse phages (<u>Kirchhelle 2019</u>).
	1949: Hygiene Institute at Frankfurt [ICEPT phages] (<u>Seifert</u> <u>1949; Schlossberger and Brandis 1950</u>), set also adopted in Kiel, Munich, West-Berlin, and Göttingen.
Italy	1950: Public health institutes in Pisa, Milan, and Palermo [ICEPT phages] (<u>De Blasi and Buogo 1952</u>).
Sweden	By 1954: Statens Bakteriologiska Laboratorium, Stockholm [ICEPT phages], previous experimental work by Lilleengen on alternative phages at Pathological-Anatomical Institute of the Veterinary College in Stockholm (Lilleengen 1948).
Belgium	By 1953: Institut Pasteur du Brabant, Brussels [ICEPT phages] (WHO Archives, B8-286-6, International Committee for Enteric Phage Typing (List of Members, 1953) (<u>WHOA 5</u>)).
Denmark	By 1953: Statens Serum Institut, Copenhagen (WHO Archives, B8-286-6, International Committee for Enteric Phage Typing (List of Members, 1953) (<u>WHOA 5</u>).
Greece	By 1967: Central Public Health Laboratory, Athens [ICEPT phages] (WHO Archives, B8-286-6, E.S. Anderson to T. Keresleidze, April 27, 1967 (<u>WHOA 6</u>)).

Portugal	By 1950: Instituto Superior de Higiene, Lisbon [ICEPT phages] (Felix 1955).
Ireland	By 1953: Department of Pathology, University College Cork (WHO Archives, B8-286-6, International Committee for Enteric Phage Typing (List of Members, 1953) (WHOA 1)).
Norway	1950: Department of Bacteriology of the State Institute for Public Health, Oslo (<u>Wallmark 1949; Felix 1955</u>).
France	1945: <i>Service des Bactériophages</i> , Institut Pasteur [AF and CY phages; ICEPT phages from 1947] (<u>Théodoridès 1985; Nicolle 1979</u>).
Austria	By 1950: National Centre for Salmonellosis, Hygiene Institute, Graz [ICEPT phages] (<u>Felix 1955</u>).
Poland	1947: Wroclaw Institute of Immunology and Experimental Therapy and Gdansk Institute of Marine Medicine [CY/ ICEPT phages] ("Obituary - Zenon Buczowski" (<u>1974</u>); <u>Lachowicz</u> <u>1957</u>); Wellcome Archives, August 1950 PP GSW F1-3, Fifth International Congress of Microbiology, Rio de Janeiro, (<u>WL</u> <u>14</u>).
Czechoslovakia	By 1950: Prague State Institute of Public Health [ICEPT phages] (<u>Raška, Mališová, and Mazáček 1950</u>).
Hungary	1949: National Centre for Epidemiology, Budapest [ICEPT phages] (<u>Pászti and Erdős 2015</u>).
East-Germany	Ca. 1950: Bezirks-Hygiene-Institut in Wernigerode (renamed Central Laboratory for Phage Typing in 1955) and Hygiene Institute, Leipzig [ICEPT phages] (<u>Rabsch 2007</u>).
Rumania	1948: Romanian National Phage-typing Centre Cantacuzino Institute, Bucharest; later additional centres including one at Iasi Hygiene School [ICEPT phages] (<u>Felix 1955; Ciuca and</u> <u>Cornelia 1957</u>).
Bulgaria	By 1954: Research Institute of Epidemiology and Microbiology, Sofia [ICEPT] (<u>Nicole 1962a</u>).
Yugoslavia (Serbia and Croatia)	By 1954: Higijenski Institut N.R. Srbije, Belgrade [ICEPT phages].
	By 1954: Bacteriology Department, Centraini Higijenski Zavod, Zagreb [ICEPT phages]] (<u>ibid.</u>).
USSR	Ca. 1947: typing centres emerge in Moscow (Mechnikov Institute and Gamaleya Institute), Khabarovsk (Epidemiology and Microbiology Institute), and Tblisi [ICEPT and USSR specific phages] (Phage Laboratory, Institute of Vaccine and Serum) (Krylova [1963] 1965; Zubkova 1956) (Wellcome Archives, PP CRA 70-82, First Bulletin: Fifth International Congress for Microbiology, page 16, Rio de Janeiro, 17-24 August 1950 (WL 14); WHO Archives, B8-286-6, Report to WHO on the work of the International Centre for Enteric Phage Typing 1964–1965 (WHOA1, 3); E. S. Anderson to T. Keresleidze, April 27, 1967 – and attached list of Laboratories served by International Centre for Enteric Phage Typing (WHOA 6).
As Israel	sia Ca. 1953: Tel Aviv [later: Arthur Felix] public health laboratory [ICEPT phages] (Wellcome Library, PP GSW D141,
	Wilson Publications, G.S. Wilson and A. Felix (September 1952) Report on the Laboratory Services of Israel. Made to the Director General of the Ministry of Health. WHO (<u>WL 18</u>) –).

	By 1973: ICEPT membership (see <u>Anderson and Nicolle 1973</u>).
India	1941/1942: phage-typing centres at Seth G.S. Medical College, Mumbai; Central Research Institute, Kasauli; Department of Microbiology, Lady Hardinge Medical College, Delhi – later at NICED, Calcutta [AF; post 1947 ICEPT phages] (<u>Banker 1955; Felix 1955, 1951];Nicole 1962a, 1962b; Anderson and Nicolle 1973</u>).
China	1938-1947: Peking Union Medical College [CY Phages (Yen) remain in use locally; by 1970s ICEPT phages primarily for use in Beijing area] [Fu, Hu, and Yang 1964; Zhang, Cao, and Zou 1996; WHO Personnel Files, Chun Hui Yen (WHOA 6)]
Japan	Ca. 1942: Kitasato Institute, Tokyo [CY phages via Beijing] 1956: National Laboratory for Enteric Phage Typing at National Institute for Health, Tokyo [post 1955, ICEPT phages via London and West-Germany] (Kawabe 1942, 1944 & 1945; Kodama, M., and Ichibayashi 1948; <u>Felix 1955</u> ; Brandis 1955; Imamura and Brandis 1955; Fukumi et al. 1967).
Indonesia	Ca. 1947/1950: Eijkman Institute, Djakarta/ Department of Parasitology and General Pathology, School of Medicine, Djakarta [ICEPT phages] (<u>Brandis 1957; Lie 1950, 1949;</u> <u>Himawan 1995; Anderson and Nicolle 1973</u>). Ca. 1973-1978: NAMRU-2 Jakarta in collaboration with Institut Pasteur [ICEPT phages] (<u>Sanborn et al. 1979</u>).
Malaysia	1971: Division of Bacteriology, Institute for Medical Research, Kuala Lumpur, Malaysia (previous typing of strains in Australia/New Zealand) [ICEPT phages] (<u>Nicolle 1962b</u>) (<u>Jegathesan 1983</u>).
South Korea	 Ca. 1962: WHO National Salmonella Centre for Korea, National Institute of Health, Seoul [ICEPT phages, previous typing via Japan] (<u>Aoki et al. 1965</u>). 1972: National Phage Typing Centre, National Institute of Health (WHO Archives, B8-286-2, Nyung Hwa Lee, Ministry of Health and Social Affairs, Republic of Korea to E.S. Anderson, January 27, 1972 (<u>WHOA 7</u>)).

Legend.

- CY: Craigie and Yen
- AF: Arthur Felix
- ICEPT: International Committee for Enteric Phage-Typing

* The list denotes the first mentioned use of phage-typing within the national borders of a country. Country names are based on the historical context. Different phage sets are denoted with acronyms (see above). In some cases, phage-typing was likely conducted before the publication of relevant results. Some countries like Uruguay do not seem to have maintained typing centres for long after receiving phages. Countries that sent *S*. Typhi samples for typing abroad but are still mentioned in ICEPT reports are not listed.

In a sign of Cold War continuities of interwar research networks (<u>Vargha 2014</u>), scientists in communist Eastern Europe also received phage-typing sets – with phages and expertise often travelling along pre-war Anglo- or Francophone networks. Eastern European versions of the ICEPT phages also reached the USSR and began to be used from around 1947 onwards. Although the USSR did not formally join ICEPT, Soviet delegates attended meetings at the 1950 International Congress for Microbiology (<u>WL13</u>). Following Colindale's nomination as WHO reference laboratory in 1960, Soviet scientists repeatedly visited London for phage-

typing courses, were provided with reagents, and used ICEPT phages to produce locally tailored typing phages (<u>Krylova [1963] 1965; Zubkova 1956; Kirchhelle et al. 2024; WHOA 1</u>).

In the US, researchers had started to type typhoid with Craigie and Yen's Canadian phages as early as 1939 (<u>Morris, Brim, and Sellers 1945</u>; <u>Henderson and Ferguson 1949</u>; <u>Lazarus 1940</u>). By 1951, they had adopted the new ICEPT methodology and established a national typing service consisting of 14 regional laboratories and the new Communicable Disease Center's (CDC) enteric bacteriology unit (<u>Kendrick et al. 1951</u>).

Outside of Europe, the USSR, and North America, phage typing was adopted more unevenly. Once again, sets and expertise spread along pre-war scientific and imperial networks. South Africa, India, Australia, and Egypt had received phage-typing sets from Felix and Craigie during the war. After 1945, laboratories in wealthier areas often established permanent typing centres of their own – and occasionally offered typing services for other countries and territories. However, many laboratories in resource –poor areas only ever adopted typing temporarily and often ended up sending what samples they had to European typing hubs. In East Asia, phage-typing was introduced twice: first via Chun Hui Yen's wartime work in Beijing and then via the post-war spread of ICEPT phages from Europe. Although China never joined ICEPT, microbiologists based at Peking Medical College reported using international phage sets from 1962 (Fu, Hu, and Yang 1964). Phage-based typhoid surveillance was reported at Beijing Medical University from the 1970s onwards (Zhang, Cao, and Zou 1996).

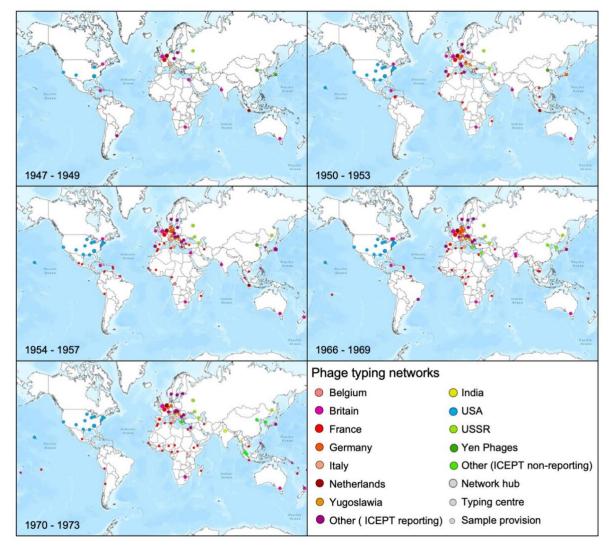


Figure 3. Expansion of phage-typing networks from c. 1947 to 1973 (Source Authors' Own)

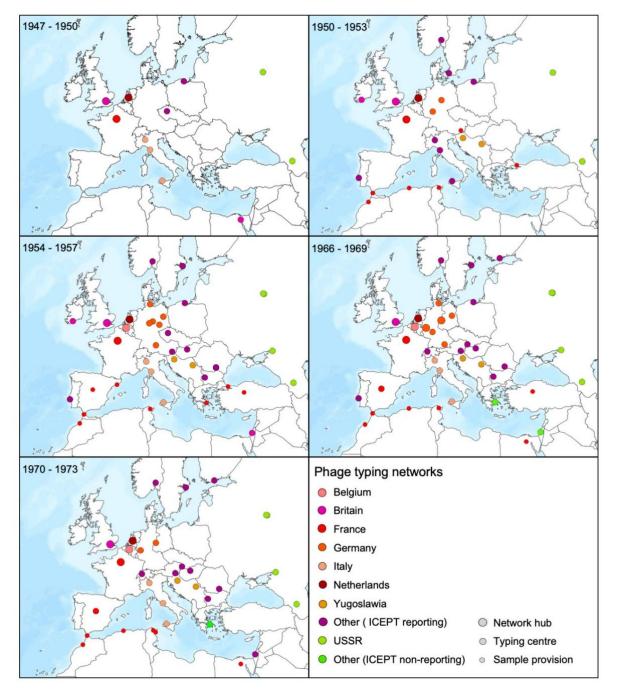


Figure 4. Expansion of phage-typing networks at the European level from c. 1947 to 1973 (Source Authors' Own).

Legend Figures 3 & 4: Location of phage-typing centres and structure of broader phage-typing networks based on ICEPT reports and phage-typing reports by individual centres. Colours denote membership to a distinct national or international network of sample provision and phage-typing. The size of a dot denotes the status of a centre within a network: hubs train phage-typers, distribute phage sets, and/or receive and type samples from other locations within the network. Typing centres have their own phage-typing capabilities but do not control or only have limited control over microbial flows within broader international networks. Sample provision denotes

locations without sustained phage-typing capabilities that supply S. Typhi samples to other typing centres within their network. Other (ICEPT reporting) centres obtained their phages and training from London, reported national typing data back to ICEPT, but were not part of broader international sampling and typing networks. The USSR, China, and other ICEPT non-reporting centres never submitted data to ICEPT. Yen Phages denotes centres using non-ICEPT phage sets originally supplied by Chun-Hui Yen. Over time, some national centres ceased to function, changed location, or resumed typing after a suspension of activities, phage-typing laboratory data was mapped using ArcGIS.

The spread of Vi phage-typing led to a significant expansion of ICEPT membership. In 1955, the organisation counted 56 national and regional reference laboratories for enteric phage typing around the world (<u>Felix</u> 1955). With notable exceptions like the USSR and China, most of these laboratories were part of ICEPT. By 1958, 32 nations had joined ICEPT (<u>Nicolle 1962b</u>; <u>Anderson 1962a</u>). Relations within ICEPT remained hierarchical. While most but not all countries in Europe and North America worked relatively independently, non-European laboratories tended to belong to distinct microbiological networks, which roughly mirrored pre-war scientific and (post-)colonial affiliations.¹¹

Within these networks, metropolitan hubs usually distributed phage kits and educated microbiologists. However, microbes and accompanying clinical and epidemiological data mostly flowed from South to North – and never from North to South. Close yet hierarchical relationships with the metropolis often remained intact after a colony's formal independence. This was particularly evident in the case of France. Closely aligned with the goals of French imperial and foreign policy (Moulin in Weindling 1995; Velmet 2020, 1–16), Pierre Nicolle's *Service des Bacteriophages* aimed to type as many samples as possible from France and the *Communauté Française* (WHOA 2). Nicolle's laboratory drew on the international network of Pasteur laboratories to source microbes from across France's (de)colonised territories as well as from countries with close historical ties to French microbiology like Venezuela, Argentina, Mexico, Chile, Brazil, and Peru. In continental Europe, the free typing services and specialist typing phages offered by Nicolle were also frequently called upon by colleagues in other countries. In contrast to interwar rivalries with US public health experts (Cueto in Weindling 1995; Moulin in Weindling 1995; Velmet 2020), the French also provided typing services and assistance to American Naval Medical Research Units (NAMRU) in Egypt and Indonesia (see figure 3).

Offering typing services was not the same as building capacity. On the surface, this was a function of the centralised nature of the *Service des Bacteriophages* and Nicolle's personal interest in the natural history of S. Typhi. However, it was also in keeping with long-standing sampling practices within the Pasteur network (<u>Moulin in Weindling 1995</u>). Despite supporting nominally independent typing centres in Venezuela, Mexico, Vietnam, Iran, Morocco, Tunisia, Iran, and Turkey (<u>WHOA 4</u>), very few of the laboratories in the French network seem to have conducted routine phage typing. Instead, they regularly sent batches of locally sourced samples to Paris for typing and analysis (<u>IPA 1</u>). By 1973, Nicolle was typing samples and pooling data from at least 20 territories across the globe (<u>Anderson and Nicolle 1973</u>). In a similar vein, Britain complied with its ICEPT and WHO mandates by sending typing sets abroad, training

¹¹ The US supported ICEPT but also maintained a distinct typing network of its own.

microbiologists, and typing foreign samples but focused limited capacity building on select Commonwealth laboratories.

In some cases, different microbiological networks were active in the same area. In Iran, the Anglo-Iranian Oil Company conducted surveys of enteric diseases close to its Abadan refinery and airlifted samples to London for typing (<u>Stewart and Tweedie 1950</u>). Meanwhile, Franco-Iranian researchers stationed at the Pasteur Institute in Teheran gathered samples for typing and epidemiological analysis in Paris (<u>Nicolle</u> <u>1962b</u>).

Their geopolitical interests, (post-)colonial sampling networks, and ability to provide phage sets and analytical expertise meant that Britain and France dominated ICEPT decision-making until the end of the millennium – a fact that was reflected in ICEPT's uniformly Franco-Anglo presidency from 1947 onwards.

Part Three: Taxonomies of Power

The hierarchical structure of international laboratory networks had important consequences for the practice of typhoid microbiology, knowledge of *S*. Typhi diversity, and the priority attached to surveying and controlling different typhoid strains. Similar to the poetic dimensions of other infrastructures, control over the means of data production allowed microbiological hubs in the Global North to proffer highly selective readings of the world as biosocial facts.

Between 1947 and 1982, ICEPT used data from its network to conduct four global surveys of *S*. Typhi phage types. The surveys produced the most extensive contemporary type diversity data for any microbe (Felix 1955; Anderson 1962a; Nicolle 1962b, 1962a; Anderson and Nicolle 1973; IFEPT 1982). ICEPT's evaluation of tens of thousands of typhoid samples revealed a significant diversity of global typhoid phenotypes and ecospheres. Between 1947 and 1964, the number of internationally recognised *S*. Typhi phage types tripled from 24 to 72 (Nicolle 1962a, 1964, 74). Some ICEPT members developed more fine-grained subtyping systems for their own territories (ibid., 82–83) and the list of international types further expanding during the 1970s (Sanborn et al. 1979). While it was rare for 'native' phage types to be completely displaced, studies showed that strain prevalence could gradually shift due to migration and intensifying trade or political ties (Nicolle 1962a; Anderson and Nicolle 1973; IFEPT 1982).

Despite these substantial achievements, resulting taxonomies and type descriptions were not neutral depictions of the world. Instead, the voluminous lists of data and type assignations gathered by ICEPT reflected and perpetuated the biosecurity context of phage-typing's birth as well as the unidirectional flows of (post-)colonial sampling networks. Historians of science and medicine have long studied activities such as mapping, surveying, collecting, and sorting as manifestations of specific power constellations and ideologically charged ways of ordering the world (Koch 2011; Engelmann 2018; Crane 2011; Harley 2009; Bangham 2014; Hopwood, Schaffer, and Secord 2010; Strasser 2011). Resulting collections and taxonomies – be they museum artefacts, administrative archives, genetic databanks, or microbial culture collections – carry within them the biases of their creation (Stoler 2002; McGovern 2021; Resch et al. 2024).

In the case of ICEPT, these biases were most obvious in the geographic disconnect between areas of intensive sampling and areas of high typhoid prevalence, which meant that resulting *S*. Typhi surveys and taxonomies were not representative of global microbial diversity or disease burdens. Between the 1950s and 1980s, most samples informing ICEPT surveys came from high- and medium-income countries with the

lowest disease burdens and not from low-income areas with the greatest typhoid prevalence (see <u>figure 5</u> and <u>figure 6</u>). In part, this imbalance reflected unequal laboratory and public health capacities. However, it also reflected – and in turn seemingly justified – the biosecurity mindset of ICEPT's founders. Although wartime destruction and displacement triggered a brief resurgence of typhoid in Europe and Japan (<u>Aoki et al. 1965</u>), the goal of most high-income countries adopting phage-typing after 1945 was to move from disease control to eradication. As discussed in Part Two, leading phage-typers argued that eradication depended on knowledge of 'native' and 'exotic' phage types, which would enable public health authorities to eliminate 'native' types and rapidly respond to the importation of new strains (<u>Felix 1943a, 1944, 1951, 1955; Anderson and Williams 1956</u>).

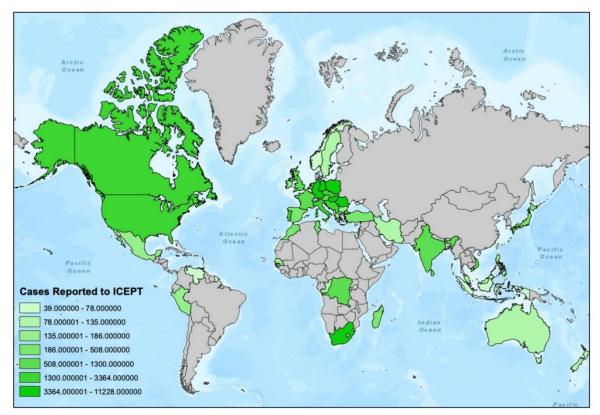


Figure 5: Geographical distribution of S. Typhi cases reported to the 1962 ICEPT survey (Source Authors' Own).

Legend: Cases were chosen as the comparator because many lower-income countries did not report the number of foci. This likely distorts reporting towards individual urban outbreaks of S. Typhi; data from the 1962 report (<u>Nicolle</u> 1962a) was mapped using ArcGIS.

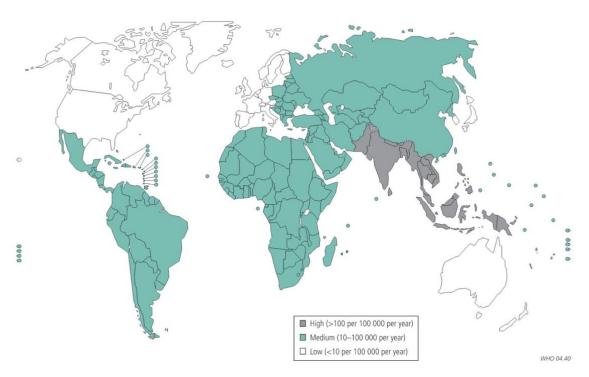


Figure 6: Geographical distribution of typhoid fever, 2000 (Source Crump et al. 2004).

Legend: Figure reused from: <u>Crump et al. 2004</u>, License: Creative Commons CC-BY 3.0 IG).

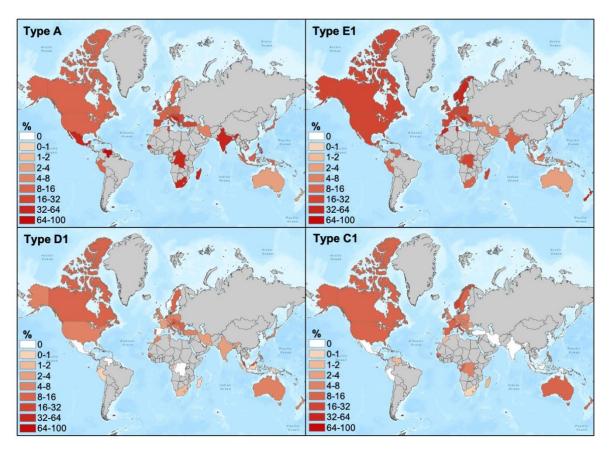
The situation was very different in poorer countries suffering the highest typhoid burdens. Many of these countries lacked robust microbiological networks and the resources to develop and sustain phage-typing expertise. Improved typhoid surveillance could have rendered invaluable assistance in differentiating enteric from other fevers, guiding preventive interventions, and tracing the spread of strains between domestic communities. However, ICEPT involvement remained primarily extractive. Instead of redressing 'diagnostic insufficiency' (Okeke 2011, 21), ICEPT leaders focused on the representative sampling of 'exotic' typhoid ecologies. Prefiguring later arguments against diagnostic capacity-building for diseases like HIV/AIDS (ibid.), it was claimed that phage-typing was useful when typhoid incidence was already so low that tracking individual outbreaks made sense but was too fine-grained for high-incidence contexts (Felix 1951).

The problems resulting from this extractive mode of sampling were manifold. In Southern locations, the 'Cinderella cycle' (<u>Okeke 2011, 171</u>) of lacking laboratory capacity justifying extractive Northern sampling and further neglect of local capacity led to distorted reporting of phage type prevalence. With the notable exception of France, data from high-income countries submitted to ICEPT often linked identified phage types to distinct outbreak foci. The idea was to avoid overreporting phage-types linked to one outbreak. By contrast, laboratory limitations meant that ICEPT reports from African, Asian, and South American countries continued to list phage types by cases and not by foci (Felix 1955; Nicolle 1962b; Anderson and Nicolle 1973). Because the limited low-income laboratory capacity was usually located close to urban healthcare centres, case reporting thus distorted ICEPT sampling toward large-scale urban

outbreaks. Coupled with the lack of rural laboratories in high-prevalence areas, this context-blind mode of sampling and reporting exacerbated the long-standing tendency to unitize Southern health problems and focus on the strains most likely to impact Northern nations via travellers or locally stationed personnel (<u>Okeke 2011, 112, 115–116, 128, 161, 170–171; Vaughan 1991</u>).

Northern biases and extractive sampling were baked into and normalised by official *S*. Typhi taxonomies. In a 1962 ICEPT report, Pierre Nicolle described the geographic distribution of the then 46 ICEPT phage types: four types were 'universal' or 'almost universal'; five types were 'exotic' with geographic descriptors associating them with 'Africa', 'Oceania' the 'Orient' (Oriental), and the 'Far East' (Extrême Oriental); three types were associated with the 'Far East' with one also occurring in South America and one in Oceania; six types were localised to certain regions or countries like Mexico, Indonesia, and Indochina; five Types were 'very rare', 'ubiquitous but rare'; two were 'extensive but not abundant'; one was 'fairly abundant'; two were 'partially ubiquitous'; four were 'rare'; and six were 'rare and widely disbursed' (Nicolle 1962a, 1962b).

Encoded within these type descriptions was an implicit acknowledgement of the geographic biases of ICEPT sampling and of the Northern biosecurity concerns it was serving. This logic becomes most obvious when one uses geographic information system software like ArcGIS to map the voluminous tabular data collected by ICEPT and critically assess the distinctions underlying 'universal' and 'exotic' or localised types. As the absence of any category designating 'European' or 'North American' strains indicates, the main criterion underlying ICEPT type assignations seems to have been whether the strain occurred in Europe and North America or not. Some phage types like A and E1 were truly universal and had a high prevalence rate in nearly all areas of the globe (Figure 7). This was, however, not so clear for other allegedly ubiquitous or semi–universal types. Phage types C1 and D1, which were described as almost universal in 1961 and as cosmopolitan in 1973 were present primarily in Europe, North America, and Australia, but far less prevalent in Asia or absent in Central America and Central Africa.



<u>Figure 7</u>. Geographical prevalence of 'universal' phage types A and E1 and almost universal phage types D1 and C1 according to the 1962 ICEPT report (Source Author's Own).

Legend: Prevalence data from the 1962 ICEPT report (<u>Nicolle 1962a</u>) was mapped using ArcGIS.

By contrast, strains like D6 or G with a high prevalence in low-income areas but less prevalence in the Global North tended to be described as localised or 'exotic'. In the case of strains with prevalence rates below five percent, those that occurred in Europe or North America were mostly assigned labels like 'very rare' or 'rare' (e.g. phage type D5, E5, E8, K, or 27). By contrast strains like phage types L1, L2, and E4 with similar prevalence in low-income areas on multiple continents but no occurrence in Europe were described 'exotic' or given regional labels like 'Far East' (see <u>figure 8</u>).

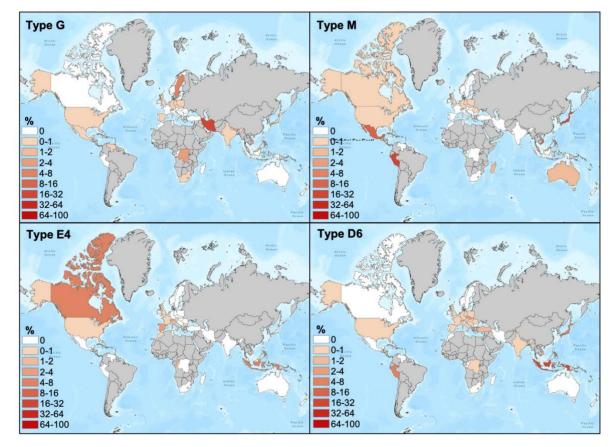


Figure 8. Geographical prevalence of 'exotic' phage types G, M, and E4 and the 'localised' phage type D6 according to the 1962 ICEPT report (Source Author's Own).

Legend. Prevalence data from the 1962 report (Nicolle 1962a) was mapped using ArcGIS.

The fact that the phenotypic taxonomy created by ICEPT phage-typing was based on mutated versions of one Vi-phage (phage II) that had originally been isolated from a Northern environment probably further biased results by providing greater 'taxonomic resolution' for S. Typhi strains that originated from geographically proximate environments. While the ICEPT phage set was able to process the majority of samples reaching reference laboratories, a substantial minority of samples remained untypable. There were three categories into which such strains were grouped. Degraded (*aliénosensible*) typhoid cultures had lost their Vi antigen while in storage or in transport and were no longer sensitive to phage lysis. Other strains naturally lacked a Vi antigen and were described as Vi-negative. A third category of strains could not be typed by phage II but proved sensitive to two other phages, which had originally isolated by Craigie and Yen. Strains that were typable by phages I and/ or IV were classified as Groupe I+IV and biochemical analysis indicated that many I + IV isolates from the same local environment were related to each other (<u>ibid., 1962b; Anderson</u>)

and Nicolle 1973; Anderson 1962a).¹² Significantly, mapping shows that Groupe I+IV strains became more prevalent the further away they were isolated from the Canadian environment in which the original Phage II had been isolated (Figure 9).

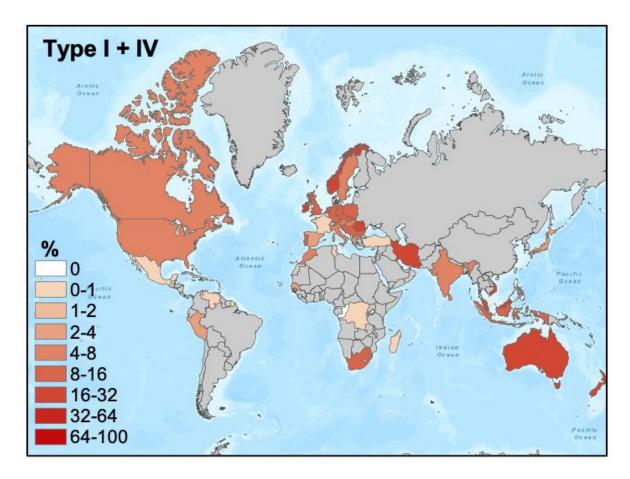


Figure 9. Geographical prevalence of Groupe I + IV strains according to the 1962 ICEPT report (Source Author's Own).

Legend. Prevalence data from the 1962 report (Nicolle 1962a) was mapped using ArcGIS.

This likely biological bias of the ICEPT phage set was exacerbated by the fact that 'Southern' laboratories lacked the infrastructure and resources to conduct representative surveys of local environments and develop new typing phages for untypable *S.* Typhi strains. During the 1950s and 1960s, most 'exotic' and 'rare' non–European strains were discovered by researchers analysing Southern samples in Northern laboratories. Of the 24 new phage types added to the international typing set between 1953 and 1958, 11 were discovered in

¹² Nicolle tried but failed to develop a more fine-grained typing system for I+IV phages (<u>IPA 1</u>).

the US, 6 in the Netherlands, 2 in Canada, 2 in the UK, 1 in France, 2 in Japan, and 1 in Italy (<u>Anderson 1962a</u>, <u>380</u>; <u>Nicolle 1962b</u>, <u>1962a</u>). Often working in resource-constrained settings and with extractive sampling networks filling microbial archives in the Global North, most Southern researchers could not conduct the time-consuming tests that were necessary to isolate, adapt, and trial new typing phages.¹³ The described lack of capacity for phage experimentation significantly reduced the chance of convincing ICEPT's Anglo-French leadership to update the international typing set with phages that had not descended from the original Phage II but were better suited to analysing distinct Southern typhoid ecologies. Hamstrung by biological, geopolitical, and laboratory capacity biases, ICEPT phage-typing ended up surveying global *S*. Typhi diversity according to Northern norms and interests.

Conclusion: Hollow Internationalism

While it is clear that twentieth-century typhoid surveys and taxonomies remained infused with the (post-) colonial gaze of the sampling networks they were produced by, it would be wrong to simplify the intentions of their creators as purely imperialist. Similar to contemporary surveys of influenza strains, human blood types, and post-1980's HIV surveillance (<u>Bresalier 2023; Bangham 2014; Radin 2017</u>), microbiologists like Arthur Felix and Pierre Nicolle were motivated by multiple drivers. This pluralism explains how post-war microbiology could be simultaneously internationalist in its rhetoric and entrench (post-)colonial North-South hierarchies of sampling and knowledge.¹⁴

Scientifically, there was genuine interest in the composition of global microbiological environments, the interplay of typhoid evolution and human history, and phages' role in bacterial genetics (Summers 1999; Creager 2002; Anderson 1955, 1962b; Brandis 1961; Anderson and Felix 1953; Boyd 1952; Lwoff 1953; Anderson 1959; Nicolle 1962b; Felix and Anderson 1951; Felix and Pitt 1951; Adams 1959). Typers were also right in arguing that better maps of global type prevalence could improve public health responses and serve as an early warning system for international challenges such as spreading AMR or large-scale outbreaks (Anderson and Smith 1972; Waldvogel and Pitton 1973; Anderson and Nicolle 1973; Anderson 1975; Kirchhelle 2020). Leading researchers openly acknowledged that existing sampling networks were insufficient to give a complete overview of type diversity outside the Global North (Felix 1955; Anderson and Nicolle 1973; IFEPT 1982). Over time, they also updated their language to account for a decolonising world. The 1973 ICEPT report tried to introduce less normative labels by using new definitions like 'cosmopolitan' – although this category remained bound to prevalence in Europe (Anderson and Nicolle 1973). By 1981, the renamed International Federation for Enteric Phage Typing (IFEPT) redefined 'exotic phage types' as types that had not previously been present in a country (IFEPT 1982).

¹³ ICEPT recognition of a new phage type depended both on researchers' ability to generate sufficient biological data and international backing from other ICEPT microbiologists.

¹⁴ Aro Velmet has highlighted a similar plurality of identities among interwar Pasteurians trying to reconcile dispassionate images of ascetic science with business interests, geopolitics, and images of French national vigour and imperial mission (<u>Velmet 2020, 80–114</u>).

However, in practice, ICEPT's commendable goal of surveying the global microbiome always contended with parallel impulses to maintain geopolitical control over microbiological networks and strategically relevant information. Domestically, Northern researchers justified typing efforts by highlighting biosecurity threats like biological warfare and the need to stop so-called exotic strains and their carriers from crossing borders and evading state control (<u>Crocker 1947; Felix 1944, 1951; Anderson 1959;</u> Nicolle et al. 1964; Waldvogel and Pitton 1973; Baine et al. 1977; Conn et al. 1972; Sharp and Heymann 1976; Brandis et al. 1967; 1972; Brandis et al. 1980). Pierre Nicolle was particularly explicit in warning about 'the dangers of an invasion of typhoid fever in Europe and North America' (Nicolle 1964, 68). In contrast to ICEPT's internationalist rhetoric (WHOA 4), phage-typing efforts thus mirrored broader trends within post-war international politics by focusing on sampling and coordination rather than sustained capacity-building beyond Northern borders (<u>Manton and Gorsky 2018; Packard 2016</u>).

The hollow internationalism of typing networks was perpetuated by phage-based taxonomies. As described by numerous scholars, taxonomies' power rests in their ability to abstract potentially endless variations of objects encountered in the world into a seemingly clear raster of standard types. Despite often being contested, this taxonomic ordering of the world allows different biological organisms to be studied as if they were the same entity across space and – barring reclassifications – time (<u>Pickstone 2000; Strasser 2011, 2019</u>). The implied universalism of taxonomies not only cloaks the power struggles involved in their creation, but also masks the ongoing exertion of geopolitical and cultural power through authoritative type assignations (<u>Tilley 2011; Curry 2021</u>).

While fully exploring all of the consequences of these imbalanced taxonomies is beyond the scope of this article, distorted readings of *S*. Typhi diversity undoubtedly contributed to an entrenched biopolitics of neglect for typhoid. With concerns about typhoid within high–income countries diminishing from the late 1950s onwards, biostatistical evaluations of data on 'normal' and 'exotic' *S*. Typhi types facilitated a binary reading of a world divided into sanitised normal and abnormal areas of exotic threat. At the national level, the seemingly value–neutral language of taxonomies justified intensified border screening of 'exotic' strains and their usually non–white carriers (Kirchhelle et al. 2019). At the international level, it redirected attention away from structural aid for high–prevalence areas towards more limited vaccine-based interventions (Webster et al. 2024; Kirchhelle Forthcoming). Taxonomies also impacted the design of the vaccines used for these interventions with scientists choosing to focus on allegedly more representative – and therefore more prestigious – universal strains than those designated exotic. Isolated in the US, the allegedly almost–universal – yet non–representative – D1 strain was first chosen to test the protective efficacy of whole–cell typhoid vaccines in the US and has been used in all human challenge studies since then (Greisman et al. 1963; Hornick and Woodward 1967; Jin et al. 2017).

The described distortions resulting from hollow internationalism are by no means limited to the now almost extinct technology of phage-typing but span the broader history of microbial surveillance. As described by Pratik Chakrabarti and Aro Velmet, large parts of bacteriology's initial promise rested on its alleged universalism (<u>Velmet 2020, 220–223; Chakrabarti 2012</u>). This universalism was especially attractive in colonial settings because it justified limited biomedical interventions based on managing microbes rather than the more complex and expensive improvement of people's health and environments. The fact that knowledge of the microbiome remained patchy and bacteriological interventions often failed in the face of complex human and non-human realities did not deter subsequent generations of microbiologists from

regularly renewing the promise of universal standards of surveillance and control. By differentiating between microbes at the strain level, researchers such as Arthur Felix hoped to move beyond previous impasses and produce comprehensive and definitive global surveys of typhoid types. However, as this paper's mix of archival research and data visualisation has shown, ICEPT's hollow internationalism meant that resulting maps and taxonomies remained incomplete, biased, and did little to generate meaningful typhoid reductions in high prevalence areas. With typhoid rates continuing to sink in the Global North, Northern microbiologists were effectively acting as scientific gatekeepers for an increasingly Southern disease. This gatekeeping has not ended.

Over the past three decades, genomic sequencing has increasingly replaced phage-typing. Sequencing has opened new horizons for the surveillance of *S*. Typhi and other pathogens: rather than analysing phenotypic phage-bacteria interactions, current typers now study variations in universal genetic code. Significant advances in sequencing and information technology mean that *S*. Typhi evolution and spread can theoretically be studied in real-time anywhere on earth (Kirchhelle, Dyson, and Dougan 2019). With high- and middle-income countries and major non-governmental funders investing in genomic surveillance, increased *in situ* sequencing and genomic data platforms such as TyphiNET (<u>TyphiNET n.d.</u>) are also reducing the importance of physical microbial exchange. Referring to similar developments in the field of influenza surveillance, some social scientists have begun to speak of a shift from territorial concepts of microbial sovereignty to more relational regimes of what Lyle Fearnley has called 'sequence etiquette' (<u>Fearnley 2020</u>) based on data exchange and acknowledgement.

However, at least in the case of non-pandemic bacterial pathogens, the new global digital infrastructures of circulating genomic code are still 'tethered' to far more patchy physical networks of laboratories and collections of live, frozen, or lyophilised pathogens (Hinterberger and Porter 2015; Resch et al. 2024). Similar to the Cold War period, much of this infrastructure remains uneven, hierarchical, and extractive. In 2023, most of the leading international hubs for typhoid research are identical to those of the phage era and are based in Europe and North America. Asian and South American economic development has strengthened local ownership of microbial data and research. Meanwhile, ownership of the usually proprietary sequencing platforms being used to generate data and of the companies servicing machines continues to primarily rest in the Global North. By contrast, laboratory surveillance in many lower income territories remains dependent on often time-limited donor funding while also contending with the fragility of local power, water, medical, and data infrastructures that remain essential to the functioning of any laboratory-based surveillance. Current disease burden studies for sub-Saharan Africa and Oceania thus continue to be based on extrapolating data from limited numbers of mostly urban sentinel sites or from proxy sources like polio monitoring and traveller surveillance and extrapolating from passive surveillance data to calculate disease incidence and type prevalence (Ingle et al. 2019; Phillips et al. 2021). However, similar to Cold War phage-based tabular surveys, resulting gaps of microbiological coverage are rendered invisible in the uniformly coloured typhoid maps published by ICEPT successors like the Lancet Global Burden of Disease reports (Stanaway et al. 2019; Ikuta et al. 2022).

The ongoing patchiness of surveillance coverage should not surprise us. While no surveillance infrastructure will ever be comprehensive, current genomic capabilities are being grafted onto a pre-existing international system of microbial control, whose hierarchical biosecurity-oriented nature was an inbuilt systems feature. Rebalancing this system requires both sustained investment in under-served areas

and acknowledgement that Southern actors will remain marginalised if the infrastructures of microbial sampling, sequencing, and analysis continue to prioritise Northern interests. Progress in closing the gap between where the 'person interpreting the data resides' and 'the place where the sample is obtained' is possible (<u>Hinterberger and Porter 2015</u>). The last decade has seen growing awareness about 'diagnostic insufficiency' (<u>Okeke 2011, 21</u>) and the need to decolonise Global Health agendas (<u>Abimbola and Pai 2020</u>). Meanwhile, the success of countries such as Indonesia in asserting sovereignty over influenza samples and international agreements such as the Nagoya Protocol have at least in theory strengthened Southern territories' ability to stake claims on microbial samples and value. Most recently, the Covid-19 pandemic has also highlighted the dangers of lacking surveillance capabilities in low-income settings and triggered new funding for innovative local wastewater-based genomic surveillance (<u>Cyranoski 2021</u>). In the case of typhoid, it can only be hoped that capacity-building and openness about entrenched asymmetries will rebalance the hierarchical microbiological infrastructures that for too long enabled Northern priorities and standards to dictate biomedical responses to an increasingly Southern disease.

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