MESA: Estrategias para mejorar el control de la TB

Moderadores: **Joan A. Caylà.** *Presidente. Fundación de la Unidad de Investigación en Tuberculosis de Barcelona.Barcelona.*
Virginia Pomar. *Unidad de Enfermedades Infecciosas. Hospital de Sant Pau. Barcelona.*

Efectividad de un centro de referencia para el tratamiento de poblaciones vulnerables con tuberculosis en Cataluña

Mario Bravo Masferrer, Joan Pau Millet, Hernán Vargas, Thaïs Balsera, Xavier Casas
Serveis Clínics. Barcelona.

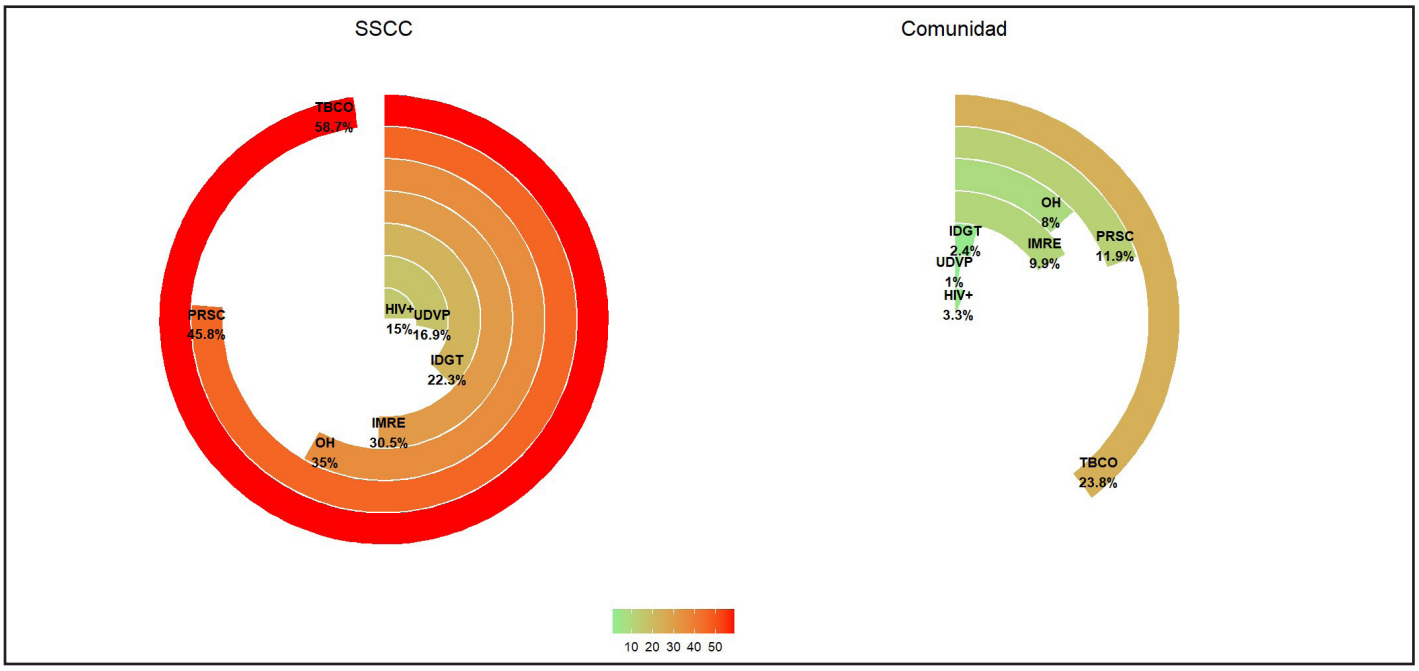
Correspondencia:
Mario Bravo
E-mail: mario.bravo.masferrer@upc.edu

Serveis Clínics (SSCC)[1] es un centro sociosanitario de Catsalut especializado en el manejo clínico y social de casos complejos de tuberculosis (TB), siendo un referente para toda Cataluña desde 1993. Fue creado con el objetivo de mejorar el control de la enfermedad y dar respuesta a la declaración de la OMS de la TB como una emergencia de salud pública a nivel global[2]. SSCC se especializa en el tratamiento y cuidado de personas mayores, menores, coinfectadas con el VIH o con comorbilidades, así como en brindar tratamiento y acogida a personas vulnerables, sin hogar, inmigrantes recientes o usuarios de drogas, quienes conforman un grupo que se ha denominado *hard-to-reach* (difícil de alcanzar o incluir) debido a las dificultades para acceder desde el punto de vista sanitario y social[3]. En colaboración con los distintos agentes del programa de TB de Cataluña y Barcelona y en coordinación con salud pública, SSCC forma parte de una red sociosanitaria para garantizar el cumplimiento del tratamiento y el cuidado de personas, que a lo largo de los años se ha convertido en una pieza fundamental para tratar a personas vulnerables con TB. El objetivo de esta ponencia es visibilizar la importancia del centro para curar las personas vulnerables con TB en Cataluña.

El equipo de investigación de SSCC ha estudiado, en un proyecto colaborativo con la *Agència de Salut Pública de Barcelona* (ASPB), las características sociodemográficas, hábitos tóxicos y factores de riesgo propios de las personas con TB tratadas en SSCC y, junto a ellos, los datos de los no ingresados de la ciudad de Barcelona como marco contextual. También se han buscado asociaciones entre características y resultados de tratamiento no deseados para comprender el beneficio de ingresar en la clínica, además de analizar la situación epidemiológica de Cataluña y sus tendencias para estimar sus necesidades en un futuro próximo.

Como centro de referencia de pacientes complejos, SSCC muestra unas prevalencias de factores de riesgo de mal cumplimiento y hábitos tóxicos mucho más elevados de lo que presentan las personas tratadas en la comunidad de la ciudad de Barcelona (Figura 1). Además, el perfil de la persona con TB ingresada ha cambiado a lo largo de los años, disminuyendo la proporción de personas que se inyectan drogas (PID) y las personas con VIH de principios de siglo a un perfil con más precariedad social, nacido en países de alta incidencia de TB, con importantes barreras idiomáticas, con mayor dependencia social y funcional, entre otras características. En todos estos perfiles se detectan características asociadas a resultados de tratamiento no deseados, como pérdidas de seguimiento o mayor mortalidad, que indican alta dificultad para su abordaje. Centrándonos en los casos de la segunda década de siglo y estudiando independientemente los casos tratados exclusivamente en la comunidad de la ciudad de Barcelona se detecta como principal característica problemática la precariedad social, la cual muestra una asociación significativa tanto con la pérdida del paciente como con su defunción. Entre las personas ingresadas en SSCC, las características asociadas a un tratamiento no exitoso a principios de siglo eran ser VIH+ o

Figura 1. Características de los pacientes tratados en SSCC y los tratados en la comunidad de la ciudad de Barcelona entre los años 2000 y 2022.



TBCO: Tabaco; PRSC: Precariedad social; OH: Alcohol; IMRE: Inmigrante reciente; IDGT: Indigente; UDVP: Usuario de droga por vía parenteral.

PID. Estudiando las personas ingresadas en la segunda década de siglo, las características con asociación significativa a un resultado de tratamiento no deseado no aparecen, mostrando así, que los clásicos factores de riesgo asociados a incumplimiento no influencian al resultado del tratamiento del paciente ingresado en SSCC.

La evolución de los últimos años del perfil de personas con TB en Cataluña muestra una tendencia al alza en la proporción de pacientes con precariedad social llegando a máximos histórico-cos en 2020 y con tendencia a seguir aumentando[4]. Siendo esta característica la principal problemática para la comunidad, el papel que puede desempeñar la clínica para tratar las personas más vulnerables resulta fundamental para avanzar hacia el mejor control de la TB. Además, SSCC se encuentra en una etapa de crecimiento, que con un proyecto de ampliación será capaz de tratar a más personas vulnerables y ofrecer un tratamiento de alta calidad para más pacientes de toda Cataluña.

Bibliografía

1. Serveis Clínics. Acceso: Nov. 19, 2022. [Online]. Disponible en: http://www.serveisclinics.com/ca/
2. La OMS declara el 'estado de emergencia' contra la tuberculosis | Sociedad | EL PAÍS. Acceso: Oct. 05, 2023. [Online]. Disponible en: https://elpais.com/diario/1993/04/24/sociedad/735602404_850215.html
3. Guidance on tuberculosis control in vulnerable and hard-to-reach populations - Publications Office of the EU. Acceso: Nov. 13, 2022. [Online]. Disponible en: https://op.europa.eu/en/publication-detail/-/publication/461d8231-18cd-11e6-ba9a-01aa75ed71a1
4. G. de Catalunya Departament de Salut. Informe anual 2020 Situació epidemiològica i tendència de l'endèmia tuberculosa a Catalunya Prevenció i control de la tuberculosi a Catalunya, 2022.

Target drug monitoring in the treatment of tuberculosis

Samiksha Ghimire

Clinical Pharmacologist. Post-doctoral researcher.
Department of Clinical Pharmacy and Pharmacology. University Medical Center Groningen. University of Groningen. The Netherlands.
Dutch Medical Ethical Review Committee. University Medical Center Groningen. Hanzeplein The Netherlands.

Correspondence:
Samiksha Ghimire
E-mail: s.ghimire@umcg.nl

In addition to the selection of the appropriate drug, the optimization of antimicrobial therapy has two pillars: pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK) describes the behavior of a drug in the patient's body. Pharmacodynamics (PD) describes the effect of a drug on the *Mycobacterium tuberculosis* (efficacy) and on the patient (toxicity). Integration of PK and PD (PK/PD) links a PK parameter together with minimum inhibitory concentration (MIC) such as AUC_{0-24}/MIC, C_{max}/MIC, C_{min}/MIC or T%>MIC to the clinical effect. Then, the optimal dose and dosing frequency is determined based on the probability of target attainment for maximum kill of Mtb bacilli or prevention of resistance. A relatively fair agreement exists in PK/PD parameters between pre-clinical (hollow fiber infection model studies of TB and Monte Carlo simulations and animal studies) and clinical studies.

In recent years, great strides have been made in exploring the PK/PD target for core anti-TB drugs (isoniazid, rifampicin, moxifloxacin, levofloxacin etc.). These drugs exhibit considerable pharmacokinetic variability. Drug dose exposure and response relationship are affected by both mycobacterial and host-related factors such as lineage-specific factors, growth phase, phenotypic and genotypic susceptibility, location and extent of TB, cavity formation, host immune function, renal and hepatic function [1]. These inter-individual pharmacokinetic variabilities in combination with differences in microbial susceptibility and host factors means that patients on the same standardized doses achieve a range of concentrations which can translate into different clinical outcomes. This is the reason why some patients get cured while others fail the intensive TB treatment and possibly relapse later.

This abstract will briefly discuss how the PK/PD target can be utilized in the clinic for individual dose optimization through therapeutic drug monitoring and quantitative drug susceptibility testing. Furthermore, the current evidence on possibilities of PK/PD based dose optimization of anti-TB drugs will be reviewed.

New recommendations suggest closely monitoring drug levels based on PK/PD for certain groups of patients[1,2]. This is especially important for those with a higher risk of not responding well to tuberculosis (TB) treatment. These high-risk groups include patients with severe gastrointestinal issues, diabetes, HIV, kidney problems, or those on dialysis[1,2]. Additionally, individuals with poor treatment response, malnutrition, or those who are pregnant might also benefit from the monitoring. The American Thoracic Society (ATS) suggests monitoring drug levels, particularly for linezolid and cycloserine/teridizone, in patients with kidney problems[1,2]. The latest guidelines from the World Health Organization (WHO) support monitoring drug levels for linezolid and fluoroquinolones, providing an updated approach to managing TB treatment[1,3].

Drug concentration driven toxicity is well known with drugs like ethambutol (ocular toxicity), isoniazid (peripheral neuropathy), pyrazinamide (hepatotoxicity), linezolid (hematological toxicity and peripheral neuropathy) and fluoroquinolone (QT prolongation), cycloserine (CNS toxicity) and are of particular concern to the clinicians[1]. Therefore, it is advised to keep drug levels below a certain threshold for these drugs. Efficacy on the other hand is also correlated with drug exposure with parameters such as AUC^{0-24}/MIC, C_{max}/MIC, C_{min}/MIC or T%>MIC. Optimal efficacy is drived by AUC/MIC for following drugs: isoniazid (567), rifampicin (271), pyrazinamide (113), moxifloxacin (110), levofloxacin (146), linezolid (100) which means that a balance needs to be striked between attaining adequate target concentrations and avoiding toxic concentrations [4]. TDM plays an important role in this. For TDM in TB, specific concentrations at certain time-points after drug intake (1,2,3,4,6 h etc.) can be measured and AUC can be estimated in blood or other alternative sampling matrices. Traditionally, AUC estimation needed at least 6-8 samples per

patient but now limited sampling strategies (LSS) have been developed using population pharmacokinetic models, and Monte Carlo simulations based on clinical data in order to provide 2 or 3 time-points, which can be used for accurate determination of the AUC[4]. This has made TDM more feasible.

The concentrations are measured using an analytical method that is able to accurately quantify anti-TB drug levels. In particular, the introduction of high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) enabled analysis of drugs in a very small sample volume (<50 microlitre) and also allowed the development of assays in alternative sampling matrices like saliva, dried blood spots, hair and urine. A multi-analyte LC-MS/MS assay is now available that includes most of the first and second line anti-B drugs. The use of dried blood spots and saliva over blood (plasma/serum) overcomes the challenges associated with conventional venous sampling[1]. The use of dried blood spot samples overcomes the stability issue experienced with blood samples. Saliva samples can be easily collected and drug levels can be analyzed by simple UV spectrophotometer; a form of semi-quantitative test which allows physicians to make informed decisions on drug dosing in the absence of high tech LC-MS/MS. This is very useful in the TB endemic rural settings which are often resource limited[5].

Drug Susceptibility Testing (DST) is like the flip side of the coin. It's crucial to make sure that the chosen treatment plan is suitable for the patient. The aim is to identify the right medication at the right dosage, ensuring it effectively controls the infecting organism and helps prevent the development of drug resistance. Currently, the World Health Organization (WHO) supports both phenotypic and genotypic DST. Phenotypic DST involves determining the Minimum Inhibitory Concentration (MIC) in both solid and liquid mediums. On the other hand, genotypic DST examines genetic mutations linked to drug resistance[1]. The MIC is incorporated in the AUC/MIC to determine if a target is achieved or not.

In conclusion, PK/PD-based TDM offers crucial insights for the optimal management and treatment of tuberculosis. By tailoring treatment based on individual patient characteristics, it significantly enhances the chances of avoiding unfavorable treatment outcomes. Unlike the previous "one-size-fits-all" approach in TB treatment, these recent developments allow for a more personalized and effective treatment strategy.

Bibliography

1. Alffenaar JC, Akkerman OW, Kim HY, Tiberi S, Migliori GB. Precision and personalized medicine and anti-TB treatment: Is TDM feasible for programmatic use? *Int J Infect Dis.* 2020 Mar;92S:S5-S9. doi: 10.1016/j.ijid.2020.01.041. Epub 2020 Jan 26. PMID: 31996324.
2. Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, *et al.* Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2019 Nov 5;200(10):e93-e142. doi: 10.1164/rccm.201909-1874ST. Erratum in: *Am J Respir Crit Care Med.* 2020 Feb 15;201(4):500-501. PMID: 31729908;PMCID: PMC6857485.
3. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 Available from: https:// apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf? ua=1.
4. Märtson AG, Burch G, Ghimire S, Alffenaar JC, Peloquin CA. Therapeutic drug monitoring in patients with tuberculosis and concurrent medical problems. *Expert Opin Drug Metab Toxicol.* 2021 Jan;17(1):23-39. doi: 10.1080/17425255.2021.1836158. Epub 2020 Nov 8. PMID: 33040625.
5. Ghimire S, Bolhuis MS, Sturkenboom MG, Akkerman OW, de Lange WC, van der Werf TS, *et al.* Incorporating therapeutic drug monitoring into the World Health Organization hierarchy of tuberculosis diagnostics. *Eur Respir J.* 2016 Jun;47(6):1867-9. doi: 10.1183/13993003.00040-2016. Epub 2016 Mar 17. PMID: 26989104.

The Future of Tuberculosis Control and Global Health

Tom Frieden
President and CEO. Resolve to save lives. USA

Correspondence:
Tom Frieden
E-mail: trfrieden@resolvetosavelives.org

Despite being nearly 100% curable, tuberculosis remains a major public health problem and is currently the world's leading infectious cause of death. Global tuberculosis control efforts were off-course prior to the emergence of COVID. Although cases and deaths had been declining, and declining more rapidly among people living with HIV co-infection since the initiation and expansion of anti-retroviral treatment, the world, even pre-pandemic, was not on track to meet most United Nations and World Health Organization targets for tuberculosis control.

The COVID pandemic caused substantial disruption in essential public health programs worldwide, including tuberculosis diagnosis and treatment. This disruption has likely set tuberculosis control back by many years, with millions of cases missed and treatment delayed or treatment interrupted. This has led to millions of new infections that will develop into active cases in the coming years.

Dr. Karel Styblo hypothesized that, even without treatment, each tuberculosis patient would infect on average 15 others and that 10% of those infected would develop tuberculosis themselves. Only half of those would be infectious, so the Ro would be approximately 0.75. Given this trajectory, tuberculosis would disappear, but left to progress naturally this would take several hundred years. The objective of tuberculosis control programs has been to accelerate the process of TB elimination.

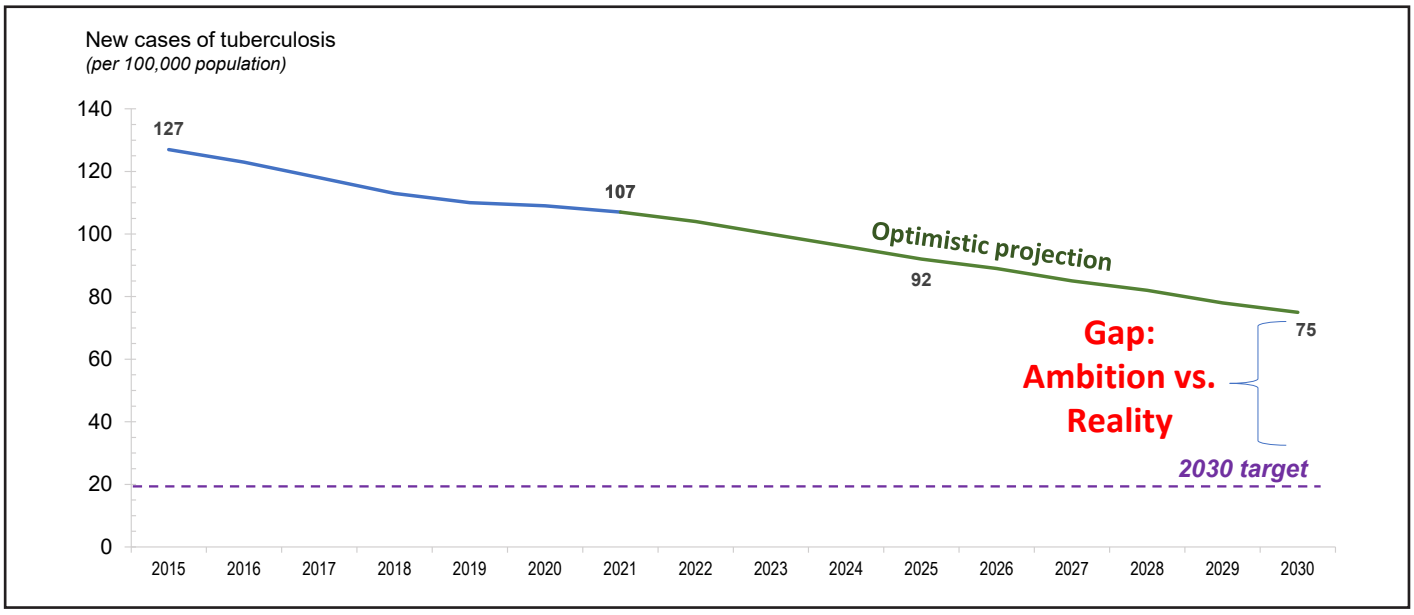
At least three fundamental shifts – in epidemiology, knowledge, and treatment – have the potential to change that clear if sobering calculation of Dr. Styblo. First, the HIV pandemic in the context of inadequately treated tuberculosis resulted in a substantial increase in tuberculosis cases. Second, a better understanding of kappa, the dispersion factor, indicates that a small proportion of cases account for most transmission (i.e., "superspreading'). Ro is a simplification of actual patterns of transmission. Third, anti-retroviral treatment of HIV and, separately, the potential to identify people with latent TB infection at highest risk for progression to active disease and treat them effectively in 1-3 months opens new possibilities for accelerating the decline in cases. If HIV and TB are rapidly and effectively treated, patients at highest risk for spreading disease will be found and treated more rapidly and their contacts protected, and if the highest risk of the large reservoir of infected people receive treatment of latent infection, it should be possible to further accelerate reduction in tuberculosis cases.

Promising new vaccines could be a game-changer for tuberculosis control. An effective vaccine for tuberculosis would undoubtedly merit a Nobel Prize, but more importantly, would save millions of lives. Progress has been very slow in part because pharmaceutical companies don't consider these vaccines to have high profit potential. Interestingly, the New York City Health Department from 1890 to 1940 was a major source of research and production of vaccines and biologicals. For public goods such as vaccines, there may be an important role for public or publicly funded research and production facilities. The current situation in which government research results in effective vaccines, such as the mRNA vaccines for COVID and other conditions, with industry reaping tens of billions of dollars of profits while charging whatever it wants, is not ethical, it does not meet the needs of patients, and it's not a responsible use of taxpayer funds.

The greatest risk to tuberculosis control is lack of implementation of effective and currently available strategies and tools. Tuberculosis control rests on three fundamental principles: prompt and accurate diagnosis, effective treatment begun immediately upon diagnosis and monitored until completion, and interruption of transmission. Effective, regular, and structured supervision of tuberculosis diagnostic and treatment facilities and their patients, combined with program management and evaluation, is essential to tuberculosis control. Focusing on these basics is the only way to accelerate progress

Tuberculosis control is fundamentally a management challenge. To manage effectively, we must treat patients as VIPs, hold the healthcare system accountable for every patient's outcome, and use data, including adoption of modern information systems, to improve performance. Tuberculosis control programs must be patient-centric. Failure to bring treatment directly to patients at no cost and no barriers to them results in many patients being

Figure 1. Global Tuberculosis Control: Far Off Track From Target.



lost to treatment, allowing their disease to become worse, spread to others, and become drug-resistant.

Forgetting is the key challenge in tuberculosis control. Political leaders forget the poor and disenfranchised, who are most likely to contract and die of tuberculosis. Health leaders forget simple, low-technology interventions and therefore neglect the core work of treatment observation, field supervision, and cohort monitoring and evaluation. Patients forget how sick they were and may stop medications when symptoms subside.

The hallmark of tuberculosis is persistence – the persistence of the *M. tuberculosis* bacillus for life in most infected people, and the persistence of reproducing bacilli during the initial weeks of treatment. This must be matched by persistence with basic tuberculosis control principles.

As the peak of the COVID pandemic passes, societies need to need get the "3 Rs" right. First, a Renaissance in public health to improve our capacity to find, stop, and prevent health threats. Second, *Robust* primary health care that is at the center of health care systems – with the amount and structure of funding sufficient and appropriate to implement effective, patient-centered, accountable primary health care. This would also improve the ability to quickly detect and completely treat tuberculosis disease and latent tuberculosis infection. Third, Resilience so individuals, families, and communities are able to better withstand and respond to health threats of all types.

A new global target of 7-1-7 for early outbreak detection, notification, and response, which has been adopted by the World Health Organization, can support a public health renaissance. Under the 7-1-7 performance standard, every suspected outbreak is identified within 7 days of emergence, is reported to public health authorities within 1 day, and is effectively responded to – as defined by objective benchmarks – within 7 days. The 7-1-7 target can help break the cycle of planning and more planning, instead using an approach of promptly finding and quickly fixing gaps in preparedness – using every outbreak or suspected outbreak to improve performance during the next outbreak.

For tuberculosis control and for global health more generally, progress will require technical rigor, operational excellence, and political savvy. Technical rigor will be important to develop and implement new vaccines, diagnostics, treatments, infection control, and other tools. Operational excellence will always be important to improve the quality of deployment of these tools. And political action will be essential, including to:

- Fund technical innovations;
- Fund operationally excellent programs and track and hold those programs accountable for progress using real-time, accurate data including on the actual experience of patients;
- Fund and sustain a broader renaissance in public health, using modern medical, management, and informatics tools;
- Make the hard choices so that primary health care truly becomes the center of our health care systems, increasing the amount of money we spend on primary health care, the salaries of primary health care staff, and the financial model so that the interests of patients, providers, and payors are all aligned to protect and improve health; and
- Support resilient populations through community-wide action, including increasing taxes on and reducing the use of tobacco, alcohol, soda, and other ultraprocessed foods;

reducing PM2.5 and lead pollution; promoting safe, active transport so walking and cycling are easy and pleasant; and changing the regulation and cost of food so what we eat and drink is healthy and nutritious, with much less sodium and much more potassium than most people currently consume.

Bibliography

- Frieden TR, Lee CT, Lamorde M, Nielsen M, McClelland A, Tangcharoensathien V. The road to achieving epidemic-ready primary health care. *Lancet Public Health*. 2023 May;8(5):e383-e390. doi: 10.1016/S2468-2667(23)00060-9.
- Cobb LK, Frieden TR, Appel LJ. No U-turn on sodium reduction. *J Clin Hypertens* (Greenwich). 2020 Nov;22(11):2156-60. doi: 10.1111/jch.14021.
- Frieden TR, McClelland A. Preparing for pandemics and other health threats: societal approaches to protect and improve health. *JAMA*. 2022 Oct 25;328(16):1585-6. doi: 10.1001/jama.2022.18877.
- Frieden TR, Lee CT, Bochner AF, Buissonnière M, McClelland A. 7-1-7: an organising principle, target, and accountability metric to make the world safer from pandemics. *Lancet*. 2021 Aug 14;398(10300):638-40. doi: 10.1016/S0140-6736(21)01250-2.
- Frieden TR, Brudney KF, Harries AD. Global tuberculosis: perspectives, prospects, and priorities. *JAMA*. 2014 Oct 8;312(14):1393-4. doi: 10.1001/jama.2014.11450.