Abstract: Throughout history, technological progress has profoundly transformed population health, but the distributional effects of these gains are unclear. New substitutes for older, more expensive health technologies can produce convergence in population health outcomes, but may also be prone to “elite capture” (leading to divergence). This paper studies the case of penicillin using detailed mortality statistics and exploiting its sharply-timed introduction in Italy after World War II. We find that penicillin reduced mean infectious disease mortality rates substantially and produced substantial convergence across disparate regions of Italy, decreasing the standard deviation of penicillin-sensitive disease mortality by approximately 60 percent. We provide evidence that these results are not explained by competing risks or the end of World War II.

JEL Codes: I10, J10, N00
1. Introduction

Technological progress in health has been a key factor in increasing life expectancy across countries (Davis 1956; Preston 1975; Easterlin 1999; Mokyr 2002; Acemoglu and Johnson 2007) and is often put forth as a solution to health problems in developing countries. Yet technological progress can also have unintended consequences for the distribution of disease. If only elites can afford a health technology, or if a technology is a private good that might substitute for public good provision, such innovation could widen health disparities, at least initially (Mosca 1939; Olson 1965; Kremer and Willis 2016; Ashraf et al. 2016). Alternatively, “breakthrough” health technologies that are inexpensive and substitute for older, more expensive ones may produce population health convergence.

In this paper, we analyze the effects of the introduction of penicillin, arguably one of the most important health technologies of the twentieth century (Tomes 1990, 1998). Discovered to kill *Staphylococcus* bacteria by Alexander Fleming in 1928 — and successfully isolated and produced by Howard Florey, Ernst Chain, and Norman Heatley in 1939 — this new “miracle drug” quickly became the first-line treatment for pneumonia, diphtheria, syphilis, gonorrhea, scarlet fever, and other infectious diseases (Dowling 1977; Levy 1992).¹ Penicillin’s achievements were preceded by those of sulfa agents, the first chemotherapy developed to fight infection and the subject of scholarship by Jayachandran, Lleras-Muney and Smith (2010), who find the introduction of sulfa drugs led to impressive reductions in maternal mortality and pneumonia deaths in the historical United States.²

We build off the Jayachandran et al. study in two ways: first, by exploring the role penicillin had on average mortality in Italy following its introduction by the United Nations in the aftermath of World War II, and second, and more generally, by documenting the effects of the technology on the distribution of health.³ Some scholars suggest that the distribution of new technologies, even inexpensive ones, often benefit the elite first (Brenzel and Claquin 1994). Others suggest that more portable technologies which do not require large scale infrastructure investments are less prone to elite capture and have considerable potential to improve population health (Acemoglu and Robinson 2008; Mosca 1939; Olson

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¹ *The Lancet* published a high-profile article in 1943 entitled “General and Local Administration of Penicillin,” describing the effectiveness of penicillin in treating wounded soldiers in North Africa (Florey and Florey 1943). Some scholars estimate that penicillin saved at least 300,000 lives during the Second World War (Dowling 1977; Levy 1992; Ratcliff 1945).

² Conybeare (1948), Loudon (1988), Mackenbach and Looman (1998) also provide suggestive evidence on the importance of antibiotics. By contrast, several studies suggest that penicillin did not have the dramatic effect commonly attributed to it (Hemminki and Paakkulainen (1976) studying Finland and Sweden, for example).

³ Sulfa drugs are distinct from beta-lactam antibiotics, of which penicillin is the first developed (Mandell, Douglas and Bennett 2010).
1965). For penicillin, this could be particularly true given that political decision-making often targeted expensive water and sanitation infrastructure — which can greatly reduce the incidence of penicillin-sensitive diseases — towards more elite neighborhoods and communities (Bigatti 2014; Massarutto 2011; Picci 2002; Troesken 2004). Finally, technological progress may be “necessary” but not “sufficient” for health convergence — institutions may be critical to ensure benefits are distributed to those most in need.

To study the distributional consequences of the introduction of penicillin, we assemble a dataset of Italian vital records spanning much of the twentieth century (Atella, Francisci and Vecchi, 2017). We use these data to estimate the contribution of penicillin to infectious disease mortality decline in Italy during the twentieth century. Focusing on the years between 1924 and 1966, we first establish its average effect on mortality by interacting the sharp timing of penicillin introduction with causes of death sensitive to penicillin, controlling for time- and region-level effects as well as regional linear time trends. We then estimate penicillin’s effect on the distribution of mortality in four ways: first, by analyzing changes in the age distribution of deaths over time, using Kolmogorov-Smirnov (KS) tests to detect significant differences in these distributions year-by-year; second, using our econometric approach akin to our framework for studying mean reductions in mortality rates, but testing for differential declines by initial level of infectious disease death rates; third, testing for $\beta$-convergence, following the literature on macroeconomic growth and economic convergence (Barro and Sala-i-Martin 1992); and, fourth, testing for $\sigma$-convergence by estimating the relationship between penicillin introduction and changes in the standard deviation of regional mortality rates (Janssen et al. 2016).

We find sharply-timed reductions in penicillin-sensitive mortality rates across Italy that closely coincide with the introduction of penicillin in 1947. There are no trend differences between penicillin-sensitive and penicillin-insensitive diseases prior to 1947, and the subsequent decline of about 0.3 deaths per thousand annually represents a 66% reduction relative to the average rate of penicillin-sensitive deaths in earlier years. Then, using all four estimation approaches, we find clear evidence of mortality rate convergence across regions of Italy. Relative to years prior to 1947, the introduction of penicillin reduced the dispersion of penicillin-sensitive mortality rates across regions by 68%, explaining 40% of all-cause convergence over this period.

We also consider two important threats to the internal validity of our analyses. The first is competing risks. Because our estimation framework relies on comparisons between penicillin-sensitive and penicillin-insensitive diseases, reductions in penicillin-sensitive deaths could mechanically increase non-communicable disease (NCD) mortality as those benefitting from penicillin live long enough to suffer and die from non-infectious causes. We show that competing risks are not a threat in practice because the decline in penicillin
sensitive death rates is present when examining a simple change over time (i.e. not making comparisons with NCDs). Furthermore, even when the sample time frame is limited to a very short window following penicillin’s debut, thereby reducing the movement of infectious disease survivors into deaths due to non-infectious causes, we still find statistically significant and medically meaningful effects. The second issue is that penicillin was introduced shortly after the end of World War II. Infectious disease mortality rates commonly surge during wartime (Erdem et al. 2011; Zapor and Moran 2005), so their decline relative to non-infectious mortality rates could partly reflect the end of conflict and regression to the mean. However, our results are similar across areas with varying degrees of war-related destruction and are robust to excluding years 1943–1945 (the years of most intense conflict in Italy) from our estimation.

The paper proceeds as follows. Section 2 provides historical background on public health in Italy and the introduction of penicillin, and Section 3 describes the construction of the dataset. Section 4 focuses on the role of penicillin for mean reductions in mortality, and examines penicillin’s contributions to population health convergence. Section 5 considers competing risks and presents other robustness checks, and Section 6 concludes.

2. Background

2.1 Early Efforts to Combat Infectious Disease Mortality in Italy

At the time of unification in 1861, life expectancy at birth in Italy was approximately 29 years, and the crude death rate was about 35 per 1,000 people (Atella, Francisci and Vecchi, 2017). In 1887, Francesco Crispi’s government introduced the country’s first sanitary reforms under the Crispi-Pagliani law. However, infectious disease deaths in Italy did not begin to decline until the early twentieth century, which historians link to improvements in municipal hygiene under provisions of the law governing water quality and sanitation in urban areas (Giovannini 1996; Giuntini 1999; Pogliano 1984). During fascist rule (1920–1943), public health initiatives targeted the so-called “triple endemic diseases”: malaria, syphilis, and tuberculosis.  

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4 The establishment of a health system is interpreted by historians as one of the most important achievements of Italian “political and moral life” at the beginning of the new Kingdom [Croce (1928), cited in Cosmacini (2005), p. 345].

5 The most important provisions focused on malaria were issued between 1923 and 1934 through a series of laws designed to arrive at a thorough land reclamation operation (bonifica integrale). The Consolidation Act on the reclamation of marshlands was approved with Royal Decree no. 3256 of 30 December 1923. Law no. 3134 of 24 December 1928, called the “Mussolini Law,” which granted financial resources to land reclamation and provided for integrations regarding the supply of drinking water and the construction of rural buildings, hamlets, and roads.
Italy’s nascent healthcare system and reforms often failed to reach its poorest members (Giovannini 1996; Giuntini 1999; Pogliano 1984). Municipal authorities were responsible for providing healthcare to the indigent, yet in practice private charitable organizations provided these services (Opere Pie, or “Pious Organizations”). A Royal Decree in 1884 established that private firms could invest in the water sector (Ermano and Massarutto 2012). Massarutto (2011) argues this decree and the ensuing privatization directed water supply towards the wealthy in urban areas. As late as the 1950s, only 52% of private houses in Italy received potable water (Doria 2010), and only 7% had all three utilities: potable water, adequate sanitation, and electricity (Bagnasco 1996).

Mortality rates in Italy declined on average during the early- to mid-1900s (see Figure 1), though wide regional health disparities in infectious disease mortality were prevalent at the beginning of this period (Figure 2, Panel A). Nationally, life expectancy at birth in Italy rose to 40–45 years — but varied by as much as 12 years across regions. These regional disparities peaked in 1925–1930, remained high until WWII, and then declined sharply at the end of the war as penicillin became available. Understanding what explains the compression of regional mortality rates is a central focus of this paper.

2.2 The Advent of Penicillin Supply in Italy

The supply of penicillin in Italy began in 1947 (Luzzi 2004). Italian patients could receive the new drug free of charge if requested by their physicians. To distribute antibiotics

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6 The law’s principles of universalism became effective only in 1978, when the Italian National Health Service System (SSN) was established.
7 The “non-poor” generally used services provided by individual private-practice doctors (medici libero-esercienti) who made home visits.
8 Modern water infrastructure in poorer southern regions was completed only in the late 1980s (Mantelli and Temporelli, 2007).
9 During the 1920s the regional variation in life expectancy at birth was almost as large as that estimated for Indian states between 2011 and 2016 — ranging from 61.5 years in Madhya Pradesh to 77 years in Kerala (Ponnapalli et al., 2013).
10 In its early stage of distribution (1945 and 1946) penicillin was available in Italy through international aid only, imported by the UNRRA (United Nations Relief and Rehabilitation Administration) channel and limited in quantity. At that time the black market was flourishing. Therefore, having enough money and connections, people could reach for the drug (the initial distribution of penicillin in Italy by the US Army started with the main intent on using it to treat the spreading of venereal diseases). To resolve this problem ENDIMEA (Ente Nazionale Distribuzione Medicinali agli Alleati) was established, which began its work on October 1st, 1944. Since January 1st, 1945, each provincial health office began to communicate to the General Directorate of Public Health (DGSP), within the Ministry of the Interior, estimates of the demand for medicines for the quarter. The DGSP, based on the requests and the availability of drugs, granted the drugs to the applicants, informing ENDIMEA to ship the product to the local private wholesalers. Once the wholesaler collected the drugs, he was responsible for the distribution of medicines to the Provincial Health Offices. The latter also had an obligation to follow the drug during the journey from the wholesaler warehouse to the pharmacies or hospitals, in order to prevent theft and illegal sales. The Italian health authorities were responsible for any shortages of medicines. In the spring of 1945 the drug became available via physician prescription, but only in the City Public Health Offices (Ufficio d'Igiene). In 1947, the pharmaceutical company “SPA Milan” became the first private Italian
supplied by the Allies, provincial offices of ENDIMEA (Ente Nazionale Distribuzione Medicinali agli Alleati, the national agency responsible for drug supply) procured drugs from the General Directorate of Public Health (DGSP) within the Ministry of Internal Affairs. Wholesalers were then responsible for the actual distribution of medicines, and Provincial Health Offices were responsible for monitoring supply chains to prevent theft and illegal sales. Provincial Health Offices were held accountable for any shortages of medicines, and pharmacists received a high margin for the sale of antibiotics, which discouraged the emergence of an underground market favoring the wealthy (Battini 1946; Luzzi 2004).  

3. Data

3.1 Vital Statistics Data

The Italian National Statistical Office (ISTAT) provides national vital statistics in annual Health Statistics Yearbooks (Annuari di Statistiche Sanitarie) starting from 1887. Vital statistics for years 1924–1955 were digitized at the region-year-cause of death level.

Harmonizing Regions. ISTAT data provides death counts for Italy’s regions over time. Due to changes in administrative regional borders over our period of investigation, we aggregated to the regional level. From 1924 until the end of WWII, Italy was organized into 18 administrative regions with only minor changes across regions. For this reason, our analysis starts in 1924. One exception is the establishment of Valle d’Aosta in September 1945. To obtain a harmonized regional dataset we treat Piedmont and Valle d’Aosta as a single region.

Thus, our sample includes the following 18 regions: Piedmont and Valle d’Aosta, Lombardy, Trentino Alto Adige, Veneto, Friuli Venezia Giulia, Liguria, Emilia Romagna,
Tuscany, Umbria, Marche, Lazio, Abruzzi and Molise, Campania, Apulia, Basilicata, Calabria, Sicily and Sardinia.\textsuperscript{15}

_Harmonizing Cause of Death._ Beginning in December 1924, ISTAT began collecting cause of death data at the individual level. ISTAT collects this information using an official reporting format (“Scheda di morte”) following international standards recommended by the World Health Organization (WHO). These individual death certificates consist of two parts. A general practitioner or coroner certifies the first part and ascribes cause. The “initial cause” – disease or trauma – is recorded, which may have led to additional complications but initiated a causal chain leading to death. Diagnostic codes are then assigned to each death using WHO International Classification of Diseases (ICD) criteria. The second part is completed by a municipal civil registrar and includes information about the demographic and social characteristics of the deceased.

Causes of death reported in Italy’s vital records change over time. We therefore use categories that can be consistently identified and tracked across all study years, effectively adopting the classification used in 1956–1957 for all years of our analysis (1924–1955).\textsuperscript{16} We then classify each of these causes that can be consistently tracked over time according to whether or not it can be treated with penicillin. Ultimately, this process yields 79 penicillin-insensitive, 15 penicillin-sensitive, and 15 unclassified diseases.\textsuperscript{17} In our analysis of cause-specific mortality we exclude unclassified deaths.

We measure destruction related to World War II using the number of military and civilian deaths directly related to war causes at the regional level that occurred between 1940 and 1945 (ISTAT 1957).\textsuperscript{18}

\textsuperscript{15} For sake of completeness, in December 1963 the region of Molise was established by splitting the “Abruzzi and Molise” into two distinct regions. This last change brought Italy to have the current administrative structure based on 20 regions.

\textsuperscript{16} The 17 causes of death are the following: infective and parasitic diseases; tumors; allergic and endocrine glands diseases; blood and hematopoietic diseases; psychic and personality disorders; nervous system diseases; circulatory system diseases; respiratory system diseases; genitourinary system diseases; complications of pregnancy; skin and tissue diseases; bones and locomotive organs diseases; congenital malformations; early childhood particular diseases; senility and pathologic states; accidents, traumatisms, and poisonings. The coding system adopted during years 1924–1955 has changed from the International Analytical Classification (IAC) to the ISTAT Intermediate Classification (IIC) adopted in subsequent years. Moreover, from 1958 onwards, there is a higher disaggregation of diseases with respect to years 1956–1957, due to the inclusion of new death-related causes.

\textsuperscript{17} The list of “penicillin-sensitive” and “penicillin-insensitive” categories of death are reported in Appendix 2.

\textsuperscript{18} The war victims are quantified according to the region of actual death, delivering a space/time quantification of war conflicts. WWII severity indicator in Italy is provided by the official publication “Morti e dispersi per cause belliche negli anni 1940–45” (The dead and the missing due to war causes between 1940–1945) (ISTAT, 1957). The intensity of war destruction was quantified based at the median. Regions above-median conflict deaths are: Piedmont-Valle d’Aosta, Veneto, Friuli Venezia Giulia, Emilia Romagna, Toscana, Umbria, Marche, Lazio, Lombardy, Trentino Alto Adige, Abruzzi and Molise, Campania, Puglia, Basilicata, Campania, Sicilia, Sardegna. See Atella, Di Porto, and Kopinska (2017) for a detailed description of the data used. WWII-related
Constructing Rates. Finally, using death counts by region, year, and cause, we construct mortality rates using data on regional populations in Italy over time. Specifically, to create population denominators, we use regional population counts from Italy’s decennial population censuses provided by ISTAT. For inter-censal years, population estimates accounting for births and deaths provides estimates of this population construction process using several sources of population data (Vecchi, 2017; see Appendix 1 for more details).19

Our final sample contains region-year-cause of death observations for years 1924–1959. Table 1 shows descriptive statistics on all-cause mortality for penicillin-sensitive and penicillin-insensitive diseases before and after penicillin introduction.

3.2 Human Mortality Database (HMD) Data

We also use national-level data on age-specific deaths from the Human Mortality Database (HMD) in two ways (HMD 2017).20 First, because the regional vital statistics do not contain information about deaths by age, precluding age-adjustment, we control for age-specific population counts.21 Second, we directly examine changes in the age distribution of deaths over time as an alternative strategy for studying mortality convergence.

3.3 Graphical Analysis

Mortality Decline by Cause. As Figure 1 shows, Italy’s total mortality rate fell substantially between 1924 and 1959. However, this decline varied dramatically by cause —

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19 Population estimates were interpolated into age bins of 0–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75, and 76+ by using known population data for years 1921–1927, 1931–1936, 1943–1950, 1953, 1957, and 1959–1961. To estimate missing population data, we broke the age bins into separate individual age columns and assumed a uniform population distribution for each age within an age bin. We interpolated missing age-specific population by taking the current year’s age-specific population and adding the previous year’s age-specific mortality to get the previous year’s age-specific population. We use the same methodology in the opposite direction by interpolating the age-specific population data of the subsequent year by taking the current year’s age-specific population and subtracting the current year’s population age-specific mortality. After all missing data was estimated, we re-aggregated the age columns into the original age bins for the population controls of our study.

20 National-level HMD estimates are constructed by HMD investigators using vital statistics, population censuses, and population estimates directly from ISTAT and from other researchers working on behalf of ISTAT. Death counts in the Italian vital statistics are based on the de facto population (“popolazione presente”) until 1980 and on the de jure population (“popolazione residente”) afterwards. Therefore, mortality rates before 1981 in the HMD are based on population estimates of the de facto population, calculated from census counts to take into account this change in the coverage of vital statistics (Glei 2015). Death counts from the vital statistics are also adjusted both to include missing military deaths during World Wars I and II and to spatially redistribute deaths by age and calendar year (Jdanov et al. 2008). For the period 1937–51, intercensal survival methods are used to derive population estimates using pre- and post-war census counts (Jdanov et al. 2008).

21 This data is also available online at: http://www.mortality.org/
and in particular, by penicillin sensitivity. Panel A of Figure 2 shows that with the official introduction of penicillin in 1947, the decline in regional mortality rates for penicillin-sensitive causes accelerated sharply. Moreover, the variance in regional death rates sensitive to penicillin became markedly more compressed beginning in 1947, with substantial convergence occurring by the mid-1950s (and persisting thereafter). Panel B of Figure 2 demonstrates regional mortality rates for non-infectious causes did not decline over the entire period — nor did their variance.22

Mortality Decline by Age. Figure 3 depicts the age distribution of period life table deaths in Italy for years between 1924 and 1955. The figure reveals substantial reductions in infant and child mortality over time (which are generally due to infectious causes, mostly penicillin-sensitive (Vercelli et al. 2014)). As a result, deaths appear to become more concentrated at older ages — a pattern consistent with convergence, although the timing of this compression is less readily evident (Section 5 investigates this issue more closely).

Standard Deviation and Average Life Expectancy: Figure 4 shows both life expectancy at birth and the standard deviation of age at death across regions (a common indicator used in the literature to measure mortality convergence and lifespan inequality (Edwards and Tuljapurkar 2005; Gillespie et al. 2014)) by year. Life expectancy at birth increases from 51.5 in 1924 to 57.6 in 1939, declines abruptly during WWII until the 1943 Italian armistice, recovers quickly to its pre-war level, and begins a steeper ascent in the post-war years as penicillin diffuses rapidly across the country. The standard deviation of age at death declines little during the pre-war period (as life expectancy at birth is rising), remains relatively constant during WWII, and then declines precipitously beginning in the late 1940s (around the time that penicillin was introduced) and throughout the post-war period. This rapid decline beginning in the latter 1940s is suggestive of mortality convergence.

Standard Deviation by Cause: Figure 5 shows the standard deviation of regional death rates separately for the all-cause mortality rates, penicillin-sensitive mortality rates, and penicillin-insensitive mortality rates over time. Before WWII, the standard deviation trajectories of penicillin-sensitive and -insensitive mortality rates were similar. Both experience disruptions during the war period, but after 1947 the standard deviation of penicillin-sensitive mortality rates across regions converges, while the standard deviation of penicillin-insensitive mortality rates diverges.

4. Estimation

22 More work is required to address concerns about the confounding role of World War II given that infectious disease deaths often exceed direct casualties due to conflict (Erdem et al. 2011; Zapor and Moran 2005). We address this issue later in Section 5.2. Further, one might also argue that WWII has favored internal migration flows from poorer to richer regions, thus contributing to higher differentials among regional mortality rates. Atella and Deb (2013) show that the phenomenon of migration within Italian regions began in earnest in 1951.
4.1 Mortality Decline

Building on graphical evidence shown in Figures 2 and 4, our empirical strategy tests for sharply-timed differential trend breaks in penicillin-sensitive mortality rates (relative to penicillin-insensitive mortality rates) coincident with the introduction of penicillin in 1947. Specifically, we estimate:

\[ m_{ict} = \alpha + \gamma_i + \delta_t + \theta_c + \beta(I_{i t}^{\text{post}} \times \text{Sensitive}_c) + X_{it} \phi + \gamma_i \times t + \epsilon_{ict}, \]  

(1)

for regions \( i \), causes of death \( c \), and years \( t \). \( m_{ict} \) is a region-cause-year specific death rate (specified both in level and natural log form). \( I_{i t}^{\text{post}} \) is a dummy variable equal to one for observations in years 1947 or later, \( \text{Sensitive} \) is a dummy variable for whether or not cause \( c \) is sensitive to penicillin, and \( X \) is a vector of covariates including interpolated population estimates in discrete age categories. We include year, region, and disease fixed effects, and our preferred specification also includes linear time trends interacted with region dummies. Standard errors are clustered by region, and we report p-values corresponding to block bootstrapped standard errors.\(^{23}\)

We also assess the temporal dynamics of the introduction of penicillin by substituting a vector of year dummy variables for \( I_{i t}^{\text{post}} \) in Equation (1):

\[ m_{ict} = \alpha + \gamma_i + \delta_t + \theta_c + \sum_j \rho_j (\text{Sensitive}_c \times I_{i t}^j) + X_{it} \phi + \gamma_i \times t + \epsilon_{ict}, \]  

(2)

where \( I_{i t}^j \) is a vector of \( j \) year dummy variables and all other variables are defined as before.

4.2 Mortality Convergence

To study mortality convergence at the national level, we first analyze changes in the distribution of age at death (Kannisto 2000; Fries 1980; Wilmoth and Horiuchi 1999). Specifically, we use Kolmogorov-Smirnov (K-S) tests to formally assess if the timing of statistically significant changes in the distribution of age at death coincides with the introduction of penicillin in 1947, comparing the distribution in each year between 1924–1954 with the last year in our sample, 1955.\(^{24}\)

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\(^{23}\) To assess the robustness of our results, we also estimate variants of specification (1), using both levels and log specifications and including region-specific linear time trends.

\(^{24}\) A two-sample Kolmogorov-Smirnov statistic is used to test whether two empirical one-dimensional distribution functions \( (F_m(x), G_n(x)) \) differ from each other. The KS statistic is defined by \( D_{m,n} = \).
Second, we test for mortality convergence associated with the introduction of penicillin using an econometric framework similar to the one that we use for estimating mean reductions in penicillin-sensitive mortality rates. Specifically, we re-estimate Equation (1), stratifying by the pre-1947 level of both penicillin-sensitive mortality rates and overall regional mortality rates.

Third, we test for $\beta$-convergence, or convergence in levels of mortality rates, following the approach of Barro and Sala-i-Martin (1992) to study convergence in Gross Domestic Product (GDP) per capita across countries. This approach assesses if regions with higher pre-1947 penicillin-sensitive and -insensitive mortality rates converged towards regions with lower mortality rates by sub-periods (before and after the introduction of penicillin, 1929–1946 and 1947–1955). Specifically, we estimate:

$$\frac{(m_{ict} - m_{ict0})}{(t - t_0)} = \alpha + \gamma_i + \beta m_{ict0} + \epsilon_{it},$$

(3)

where $m_{ict0}$ is the mortality rate in region $i$ due to cause $c$ in initial year $t_0$ ($t_0 = 1924$ for the first sub-period, and $t_0 = 1947$ for the second sub-period) and $\beta$ is the parameter of interest.

Finally, we test for $\sigma$-convergence, or convergence in the standard deviation of mortality rates, across regions of Italy by re-estimating Equation (1) using the standard deviation of cause-specific mortality rates by region as the dependent variable (Janssen et al. 2016; Young et al. 2008).

5. Results

5.1 Mortality Decline

Table 2 reports results obtained by estimating Equation (1). Conditioning on year, region, and disease fixed effects as well as the regional age distribution, mortality rates among diseases sensitive to penicillin relative to those insensitive fell by approximately 0.3 per thousand (and is statistically distinguishable from zero, $p < 0.01$) with the introduction of penicillin. Relative to the mean mortality rate among due to these causes prior to 1947 ($0.469$, see Table 1), this represents a reduction of 58%. Column 2 adds region-specific linear time
trends. In both cases, the estimate of $\beta$ is robust, with the mortality rate decline associated with the introduction of penicillin remaining at about 0.3 per 1,000. Columns 3 and 4 repeat this estimation for log mortality, showing robust reductions in penicillin-sensitive mortality rates.

Figure 6 then examines the dynamic pattern of mortality decline associated with penicillin introduction in Italy, showing estimates and 95% confidence intervals for each year-specific $\rho_j$ in Equation (2). Prior to the introduction of penicillin, there is little evidence of pre-existing declines in penicillin sensitive mortality rates (relative to insensitive ones). Year-specific estimates drop with the introduction of penicillin in 1947 and become negative and statistically different from zero by 1948 (and in all subsequent years) with the diffusion of penicillin. By the end of our study period in the late 1950s, these year-specific estimates approach a decline of 2.8 per 1,000 deaths.

5.2 Mortality Convergence

Figure 7 first shows year-by-year K-S $p$-values for tests of differences between each year’s distribution of age at death against the distribution in 1955 (the last year in our sample). These $p$-values remain constant at nearly 0 for all years prior to the introduction of antibiotics, indicating strongly significant differences from 1955 — and then beginning in 1947, these $p$-values rapidly rise to 1 (indicating no difference from 1955). This sharply-timed compression in Italy’s age distribution of deaths is highly consistent with the introduction of antibiotics leading to convergence in mortality rates.

Table 3 reports estimates obtained from Equation (1), stratified by level of penicillin-sensitive mortality rates prior to 1947 (above and below the median). The first and second columns show that after 1947, penicillin-sensitive mortality rates declined more in regions with higher (above median) initial rates (by 0.29 per 1,000) than in those with lower (below median) initial rates (0.26 per 1,000) — and significantly so.26 Compared to the mean of the pre-1947 penicillin-sensitive cause-specific mortality, these changes represent reductions of 61% and 55%, respectively.

Finally, Table 5 reports $\beta$-convergence estimates from Equation (3). Comparing penicillin-sensitive mortality rates before vs. after the introduction of penicillin, the estimate of $\beta$ is almost four times greater after penicillin introduction (-0.075 vs. -0.021). Alternatively, for penicillin-insensitive mortality rates, the estimate is not statistically

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26 We formally test for this difference by pooling the sample and testing the significance of the three-way interaction between the pre/post-1947, penicillin-sensitive/-insensitive, and above/below median level of penicillin-sensitive mortality rates prior to 1947 (p-value < 0.01).
significant prior to 1947 — and is positive and statistically different from 0 afterwards, suggesting divergence in penicillin-insensitive mortality rates.

5. Identification and Threats to Validity

5.1 Competing Risks

An important issue for interpreting our empirical estimation is the role of competing risks (see Honorè and Lleras-Muney 2006). Specifically, the reduction in infectious disease mortality due to the introduction of penicillin should mechanically increase non-communicable disease (NCD) mortality as those benefitting from penicillin die from non-infectious causes. This phenomenon can influence our estimates given that we compare penicillin-sensitive vs. penicillin-insensitive death rates over time. In this section we study the influence that competing risks has on our estimation of both mean mortality decline and mortality convergence in Italy. In general, we show that the influence of competing risks on our estimates depends on the relative levels of penicillin-sensitive and penicillin-insensitive mortality rates during our study period.

We consider the role of competing risks in our estimation of mean mortality decline in Italy. We note that our difference-in-differences estimator, which compares the decline over time in infectious vs. non-communicable diseases (NCD), can be written as follows: \( \beta = (C' - C) - (N' - N) \), where \( C \) is communicable disease, \( N \) is non-communicable disease and prime indicates the post-Penicillin period. The observed \( (N' - N) \) in the presence of competing risks is more positive than in the absence of competing risks. Specifically if penicillin drug \( d \) is introduced, then the probability of death from all types of diseases \( q \) is: 
\[
q_{t+1} = p_c(d_t) + (1 - p_c(d_t)) \cdot p_n(d_t),
\]
where \( p_c \) equals the probability of death from communicable diseases and \( p_n \) is the probability of death from non-communicable disease and we assume that only those who survive infectious disease mortality, \((1 - p_c(d_t))\), are stricken with non-communicable ailments. We also allow for the possibility – which bears out in our empirical work – for penicillin to have a direct negative effect on mortality. Differentiating with respect to \( d \) yields:
\[
\frac{\partial q}{\partial d} = \frac{\partial p_c}{\partial d} - \frac{\partial p_c}{\partial d} p_n(d_t) + (1 - p_c(d_t)) \frac{\partial p_n}{\partial d}.
\]

The first term represents the “first-order” pharmacological effect of penicillin – to reduce deaths from communicable disease (i.e. \( \frac{\partial p_c}{\partial d} < 0 \)). The second term represents

\[27\] Technically, if competing risks is a problem, it amounts to a violation of the Stable Unit Treatment Value Assumption (SUTVA), which is necessary for unbiased estimates in a difference-in-difference framework such as ours.
competing risks – it is positive and reflects how the probability of death from NCD increases as more (presumably lower health stock) individuals survive an infectious death only to die from non-infectious ailments. The last term is a “second order” spillover effect: although penicillin does not treat chronic disease directly, it provides resilience to the immune system and the latter is important for combating cancer and other non-infectious causes.

Assuming no competing risks or indirect effects of penicillin, our estimated $\beta = -\frac{\partial p_c}{\partial d}$. In the presence of competing risks, $\beta_{cr} < \beta$, introducing bias in favor of detecting a negative effect of penicillin introduction on mortality. In the case of only indirect effects $\beta_i > \beta$, leading our difference-in-differences estimate to be overly conservative. In the presence of both effects, the sign is difficult to determine ex ante. However, over time, as penicillin diffuses and more individuals are spared death from infectious causes, the competing risk term would likely come to dominate the second order spillover effect – though so too would the first order effect.

Motivated by the above discussion, we estimate the effect of penicillin on sensitive (i.e. infectious) and insensitive (i.e. NCD) causes in a pre vs. post framework and using the full vs. a truncated time period. The results, gathered in Table 4, demonstrate that, in the three years following the introduction of penicillin, both Sensitive and Insensitive mortality decline (row (2) columns (3) and (4)) though it is much larger for the former. Over time, the effect of penicillin introduction on insensitive causes is more positive, reflecting the competing risk problem, yet the magnitude of this change is slight— and dominated by the direct effect of penicillin on mortality. When turning to sigma convergence, there is no major concern for competing risks in any specification: convergence is limited to infectious causes.

5.2 The End of World War II

Another potential concern with our results is the influence of the end of World War II on infectious disease rates. Because infectious disease mortality rates commonly surge during wartime (Erdem et al. 2011; Zapor and Moran 2005), their decline relative to non-infectious mortality rates could partly reflect the end of conflict. Figure 2 (Panel A) provides at least some prima facie evidence that this is not an important concern in our case — mortality rates sensitive to penicillin are declining until 1930, generally remain stable through 1945 (rather than rising), and then resume their decline. However, we probe this issue further in two ways.

First, we test for differential penicillin effects in areas with varying degrees of war-related destruction. Specifically, we re-estimate Equation (1) separately for regions with above- and below-median degrees of war intensity, measured using conflict-related mortality
rates between 1940 and 1945. Columns 3 and 4 of Table 3 report estimates separately for regions with higher and lower intensity of exposure to WWII. In general, the penicillin effect is larger in areas with lower war intensity (0.33 per 1,000) relative to those with higher war intensity (0.29 per 1,000), and this difference is statistically significant.

Second, we simply exclude years 1943–1945 (the years of greatest conflict in Italy) from our sample and again re-estimate Equation (1). Columns 5 and 6 of Table 3 show these results — the estimates are statistically equivalent to those that include these years.

6. Conclusion

Although technological progress in health has produced dramatic gains in life expectancy around the globe over the past century, it can also have unintended consequences for the distribution of disease. Health technologies that are inexpensive and substitute for older, more expensive ones may lead to population health convergence, but they could also disproportionately benefit elites, widening health disparities. Notably, there has been little empirical evidence to date on the consequences of major new health technologies for the distribution of health in populations.

Studying the seminal case of penicillin and focusing on Italy using newly digitized vital statistics over several decades, we find that the introduction of penicillin not only reduced average infectious disease mortality rates dramatically (by 58%), but it also led to a substantial reduction in the variance of mortality rates across Italian regions. Specifically, the standard deviation in the age of death fell by nearly eight years after the introduction of penicillin — a decline of 27%. Our findings relate to the scholarship of researchers investigating post-World War II health convergence across countries, such as Acemoglu and Johnson (2007) and Angus Deaton (2006), we find that the distribution of penicillin, at least in Italy, played an important role in such convergence and suggest an important role for point-of-care technologies in reducing health inequalities.

28 This data is available in “Morti e dispersi per cause belliche negli anni 1940–45” (ISTAT, 1957) and is also online at https://lipari.istat.it/digibib/causedimorte/IST3413mortiedispersipercausebellicheanni1940_45+OCRottimizz.pdf.

29 We test for the significance of the difference between the coefficients obtained in the separate models by pooling the samples used in both models, and specifying a triple interaction that includes an indicator for high and low destruction. The coefficient for this interactions term was statistically significant (p-values < 0.01).
REFERENCES


Human Mortality Database (HMD). University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de (data downloaded on Jan 28th, 2017).

ISTAT. 1957. “Morti e dispersi per cause belliche negli anni 1940–45.” Rome.


Technological Progress and Health Convergence: The Case of Penicillin in Post-War Italy

Figures and Tables

**Fig. 1** All-cause mortality rates across all regions in Italy, 1924–1955. The unit is number of deaths per 1,000 people. *Source: ISTAT*
Fig. 2 Penicillin-sensitive (Panel A) and penicillin-insensitive (Panel B) disease mortality rates by region in Italy, 1924–1955. The unit is number of deaths per 1,000 people. Source: ISTAT
Fig. 3 Period life-table distributions of age at death in Italy for selected years between 1924 and 1955. The unit is the logarithm of the probability density of deaths. Source: Human Mortality Database (HMD)
Fig. 4 Life expectancy at birth and standard deviation of age at death in Italy, 1924–1955. The trajectories of the life expectancy at birth (left-hand side scale), and the standard deviation of age at death (right-hand side scale) are based on the distributions of age at death from Fig. 3.
Fig. 5 Standard deviation (SD) of all-cause, penicillin-sensitive, and penicillin-insensitive disease mortality in Italy, 1924–1955. The figure shows absolute levels of the SD by age grouped in approximately 5-year bins. For the decade of 1940, we consider two age groups using 1947 as a cutoff to illustrate the effect of the introduction of penicillin in that year.
Fig. 6 Penicillin-sensitive disease regression coefficients by year (log mortality), 1924–1955. The figure shows regression coefficients for penicillin-sensitive diseases by year, pre-1947 and post-1947. The outcome is log mortality per 1,000. Regression included year and region fixed effects, disease fixed effects, region-disease specific trends, and an interpolated population estimate for age bins 0–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75, 76+. Standard errors are clustered by region.
Fig. 7 Kolmogorov-Smirnov (KS) test of the equality of age at death mortality distributions in Italy, 1924–1958. The figure illustrates the significance level (p-value) of the KS test for the equality of mortality distributions depicted in Fig. 3, using the distribution of 1955 as the baseline.
Table 1 Descriptive statistics comparing cause-specific mortality before and after 1947

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin-Sensitive Cause-Specific Mortality (per 1,000)</td>
<td>N=3,726, Mean=0.469, SD=0.652</td>
<td>N=1,475, Mean=0.189, SD=0.266</td>
</tr>
<tr>
<td>Penicillin-Insensitive Cause-Specific Mortality (per 1,000)</td>
<td>N=11,093, Mean=0.237, SD=0.510</td>
<td>N=4,622, Mean=0.217, SD=0.518</td>
</tr>
</tbody>
</table>

**Notes:** The table reports descriptive statistics on the penicillin-sensitive and -insensitive specific mortality from 1924–1946 and 1947–1955. Cause-specific mortality is the number of deaths per 1,000 people. **Source:** ISTAT.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cause-Specific Mortality per 1,000</th>
<th>Log Cause-Specific Mortality per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>Sensitive*Post</td>
<td>-0.272***</td>
<td>-0.272***</td>
</tr>
<tr>
<td></td>
<td>(0.008)</td>
<td>(0.009)</td>
</tr>
<tr>
<td>Block Bootstrap SE</td>
<td>(0.008)</td>
<td>(0.008)</td>
</tr>
<tr>
<td>Block Bootstrap p-value</td>
<td>{0.002}</td>
<td>{0.002}</td>
</tr>
<tr>
<td>Observations</td>
<td>20,898</td>
<td>20,898</td>
</tr>
<tr>
<td>R-squared</td>
<td>0.867</td>
<td>0.868</td>
</tr>
<tr>
<td>Year FE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Region FE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Disease FE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Region Trends</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No. Clusters</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

Notes: The table presents coefficient estimates for the regressions of cause-specific mortality per 1,000 on a dummy variable for disease specific penicillin-sensitivity equal to 1 starting from 1947. In columns (1) and (2) cause-specific mortality per 1,000 is in levels. In columns (3) and (4) cause-specific mortality is in logs. All columns include year, region, disease fixed effects (FE), and interpolated population estimates for age bins 0–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75, 76+. Columns (2) and (4) additionally include region-specific trends. Standard errors (SE) in parentheses are clustered by region. Block bootstrap p-values are indicated in curly brackets.
Table 3: Regression results by median of pre-1947 characteristics in Italy, 1924–1955

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sensitivity to WWII Mortality</th>
<th>Approach 1: Varying Degrees of War-Related Destruction</th>
<th>Approach 2: Same as Columns (1) and (2), but Excluding Years Between 1943–1945</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Above the Median of All-Cause Pre-1947 Mortality</td>
<td>Below the Median of All-Cause Pre-1947 Mortality</td>
<td>Regions with High Destruction</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
</tr>
<tr>
<td>Sensitive*Post</td>
<td>-0.287***</td>
<td>-0.257***</td>
<td>-0.257***</td>
</tr>
<tr>
<td></td>
<td>(0.012)</td>
<td>(0.011)</td>
<td>(0.011)</td>
</tr>
<tr>
<td>Block Bootstrap SE</td>
<td>(0.011)</td>
<td>(0.010)</td>
<td>(0.010)</td>
</tr>
<tr>
<td>Block Bootstrap p-value</td>
<td>{0.002}</td>
<td>{0.004}</td>
<td>{0.004}</td>
</tr>
<tr>
<td>Observations</td>
<td>10,484</td>
<td>10,414</td>
<td>10,414</td>
</tr>
<tr>
<td>R-squared</td>
<td>0.875</td>
<td>0.901</td>
<td>0.899</td>
</tr>
<tr>
<td>Year FE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Region FE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Disease FE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Region by Year FE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Region Trends</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes: The table presents coefficient estimates for the regressions of cause-specific mortality per 1,000 on an indicator variable for disease specific penicillin-sensitivity after year 1947 in comparison to the pre-1947 regional mortality (columns 1-2), and in regions with high and low WWII destruction above the median (columns 3-4). High and low cutoffs are determined respectively by being above and below the median of the given sub sample mortality. Columns 5 and 6 present coefficient estimates for the regressions of annual change of cause-specific mortality per 1,000 on the region-cause specific mortality at a baseline year, based on the first sub-period (1924–1946) and for the second sub-period (1947–1955), respectively. The baseline year is 1924 for the first sub-period, while it is 1947 for the second sub-period. The values in parentheses represent robust standard errors (SE). We test the statistical significance of the difference between the coefficient estimates from columns (1) vs. (2), (3) vs. (4), and (5) vs. (6) by pooling the samples from the corresponding models and looking at the significance level of the estimate of a triple interaction term, that we construct using the indicator variables for disease specific penicillin-sensitivity, post-47 level of mortality, and the corresponding characteristic [e.g., for columns (1) and (2), the interaction term using the pooled sample is Sensitive*Post*(High Penicillin-
Sensitive Mortality)]. Cause-specific mortality per 1,000 is in levels. All columns include year, region, disease fixed effects, region-specific trends, and an interpolated population estimate for age bins 0–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75, 76+.

Standard errors in parentheses are clustered by region. Block bootstrap p-values are indicated in curly brackets.

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Standard Deviation (Sigma-convergence)</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category</td>
<td>Sensitive (1)</td>
</tr>
<tr>
<td>Post (Full Sample – end 1955)</td>
<td>-0.113***</td>
<td>-0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.014)</td>
</tr>
<tr>
<td>Post (Truncated Sample – end 1950)</td>
<td>-0.089***</td>
<td>-0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.014)</td>
</tr>
<tr>
<td>Difference in Post Coefficients (1955-1950)</td>
<td>-0.024</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Notes: OLS regressions collapsed across deaths within region-years on an indicator for post introduction of Penicillin, region fixed effects, population in various age categories and linear time trends. The outcome in columns (1) and (2) is the standard deviation in mortality for sensitive and insensitive diseases, respectively. The outcome in columns (3) and (4) is the level of mortality from sensitive and insensitive diseases, respectively. Each cell in rows (1) and (2) reports the coefficient on the “post” indicator. The sample varies by row, extending over the entire analytical time period in row (1) and truncating in 1950 in row (2). Row (3) reports the difference between the full and truncated sample values. If competing risks are driving the results, the effects in row (2) should be considerably less negative in row (1), columns (2) and (4), due to individuals in the lowest part of the health distribution surviving infectious disease due to the introduction of Penicillin but dying at higher rates a few years later from non-communicable mortality.
Table 5 Regression results for β-convergence by high vs. low penicillin-sensitive mortality

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Penicillin-Sensitive Mortality</td>
<td>Low Penicillin-Sensitive Mortality</td>
</tr>
<tr>
<td>Baseline mortality (1924 or 1947)</td>
<td>-0.021***</td>
<td>-0.002</td>
</tr>
<tr>
<td></td>
<td>(0.001)</td>
<td>(0.002)</td>
</tr>
<tr>
<td>Observations</td>
<td>162</td>
<td>424</td>
</tr>
<tr>
<td>R-squared</td>
<td>0.913</td>
<td>0.059</td>
</tr>
<tr>
<td>Region FE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes: The table presents coefficient estimates for the regressions of annual change of cause-specific mortality per 1,000 on the region-cause specific mortality at a baseline year. Columns 1 and 2 show results for the first sub-period (1924–1946), and columns 3 and 4 for the second sub-period (1947–1955). The baseline year is 1924 for the first sub-period, while it is 1947 for the second sub-period. The values in parentheses represent robust standard errors.