Modern Medicine and the 20th-Century Decline in Mortality: Evidence on the Impact of Sulfa Drugs

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Historical improvements in life expectancy

The evolution of life expectancy: England 1580–1996. Sources: Wrigley and Schofield (1981) for 1726–1871 and Human Mortality Database (2003) for 1876–1996.

Mortality decline in the 20th century

- U.S. mortality rates fell by 74% in the 20th century — 30 year increase in life expectancy
- Most of this increase was in the first half of the century
- What caused these gains?
- Leading view is that improvements are due to rising living standards, better nutrition and public health initiatives (e.g., water supply, sanitation, household hygiene campaigns)
- McKeown 1976, McKinlay and McKinlay 1977, Fogel 1994, Preston 1996, Cutler and Miller 2005

Role of medicine in mortality declines

- Evidence that medical innovation played a role in the second half of the century
- Historical epidemiologists have argued that mortality declines precede major medical innovations $\rightarrow$ General view is that medicine did not play a big role in first half of century
- Others disagreed but did not test/show a role of medicine
- This paper: Examine impact of the introduction of sulfa drugs in the mid-1930s

Why study sulfa drugs?

- Important discovery: First medicine effective against pneumonia, puerperal fever (40% of maternal mortality), and other major killers
- Relatively neglected in history
- Useful features for empirical research
  - Rapid diffusion (before-after analysis)
  - No other major health innovations at the time
  - Affected some infectious diseases but not others

Treatment of infectious diseases prior to 1935

- Infectious diseases treated with immunotherapy
  - Animal serum (passive immunization) for those who were sick
  - Vaccines (active immunization) as prevention
- Serum led to many complications so rarely used, but progress on vaccines (rabies, diptheria)

Advent of chemotherapy

- Use of chemicals to treat disease began in early 20th century
- A few unsuccessful drugs against urinary infections
- In 1909, after 6 years of research on organic compounds, found one that treated syphilis
- Launched "chemotherapy," i.e., systematic search for chemicals to treat disease
- Beginning of modern pharmocology
- Another breakthrough was a chemical compound to treat malaria

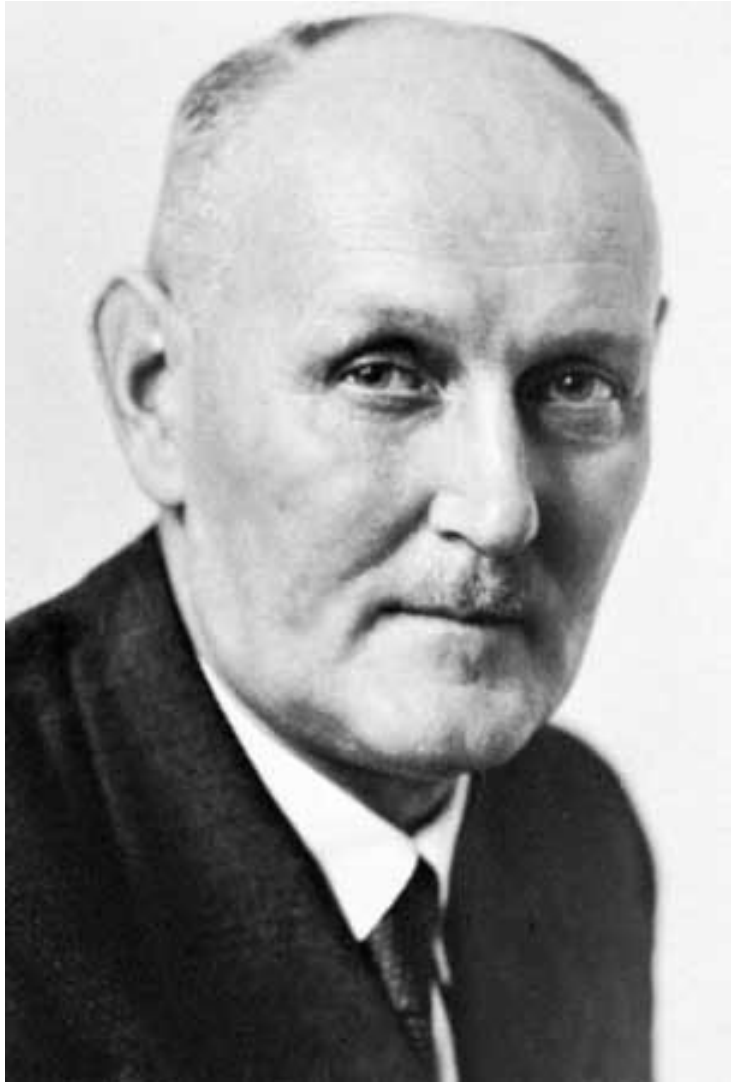
Research into sulfa drugs

- In 1927, the giant German chemical cartel I.G. Farben decided to screen for antibacterial potential the textile dyes it was producing
- Hired Gerhard Domagk, a medical doctor and university professor to lead the project
- Domagk focused on a class of dyes that attach strongly to protein in fibers or leather, reasoning that they might also attach themselves to the protein in bacteria, inhibiting if not killing them
- In 1932, Domagk was studying "Prontosil," a red dye compound
- Successful in treating mice and rabbits injected with streptococci

Use of Prontosil as a drug for humans

- First use of Prontosil on humans is unclear, may have been Dogmagk using it for his sick daughter
- Prontosil became the first successful sulfa drug (and first successful chemical to treat bacterial infections)
- Findings not published until 1935

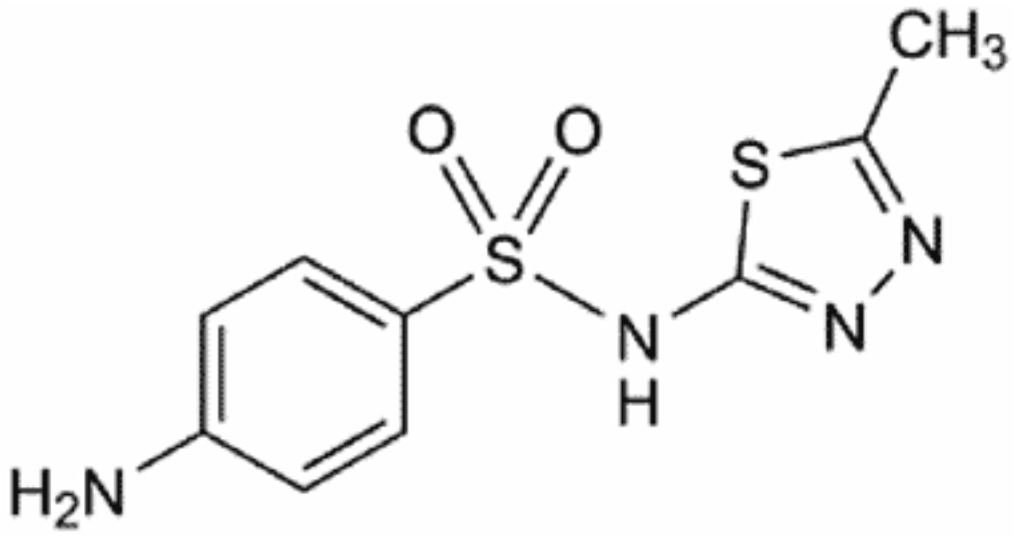
Gerhard Domagk



Awarded 1939 Nobel Prize, but could only accept it in 1947

Active ingredient in Prontosil

- In 1935, after Domagk's findings were released, researchers at the Pasteur Institute showed that the active molecule in Prontosil was sulfonamide



Intellectual property rights to sulfa drugs

- Structure of sulfonamide had been documented in the doctoral thesis of an Austrian chemist, Paul Gelmo, in 1908
- Therefore, anyone could produce sulfonamide
- Production and clinical testing of sulfonamide began on a large scale almost immediately

Clinical trials

- First major clinical trial was in 1936 in Queen Charlotte's Hospital in England
- Prontosil given to 38 women with puerperal fever (complication from childbirth caused by stretococcal infection)
- 8% mortality among treated patients versus 24% in untreated patients
- Published in Lancet in June 1936
- Results replicated and in England and elsewhere

Clinical trials and diffusion to the U.S.

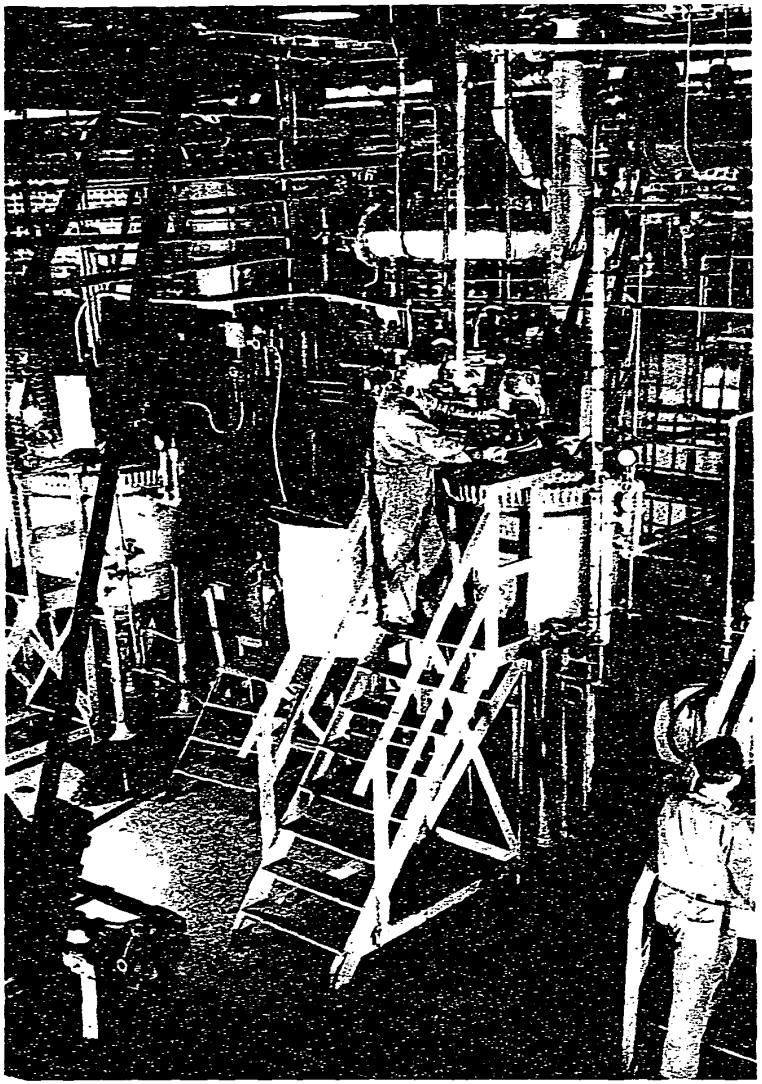
- First used in 1935 to treat a child with meningitis at Babies Hospital in NYC
- Clinical trials for pneumonia and scarlet fever done at Johns Hopkins and Western Pennsylvania Hospital
- Also shown to be effective against gonorrhea and erysipelas

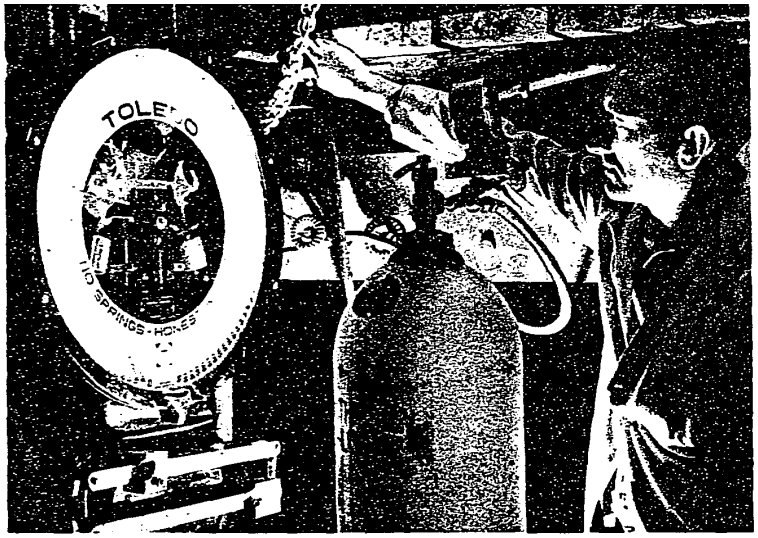
Received attention in the U.S.

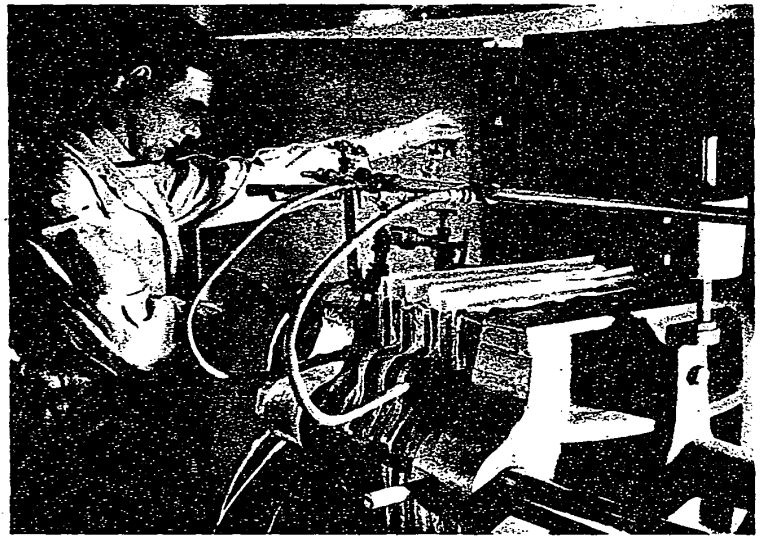
- Media created enthusiasm for sulfa drugs
- Became widely known to the public after FDR's son was cured of a deadly stretococcal infection in December 1936
- By 1941, 10 to 15 million people were treated with sulfa drugs annually
- Eclipsed by penicillin in the 1940s

EARLY in 1935 Professor G. Domagk, chemotherapist of the German chemical trust, startled the medical world with the announcement that he had discovered a chemical which kept mice alive after they had been inoculated with streptococci—deadly germs strung in chains. If verifiable this was the most important advance ever made in the treatment of a whole series of infectious diseases ranging from septic sore throats and erysipelas to puerperal (childbirth) fever and peritonitis.

Last week came the news from Boston that Dr. George Loring Tobey Jr. had saved Franklin D. Roosevelt Jr. from dying of streptococcus infection by administering prontylin, one of two related chemicals that Domagk had successfully tested on mice. Thus was the general public made aware of an outstanding discovery in medicine.







"Duplicating nature in glass vessels"—Manufacturing the sulfa drugs which are revolutionizing the practice of medicine.

The Growing Miracle of Sulfa Drugs

By Waldemar Kaempffert

New uses are constantly found for these chemical products. Their history and current development foster the belief they will revolutionize medical practice.

THE Army and Navy surgeons were prepared when the Japanese swooped down on Pearl Harbor on Sunday

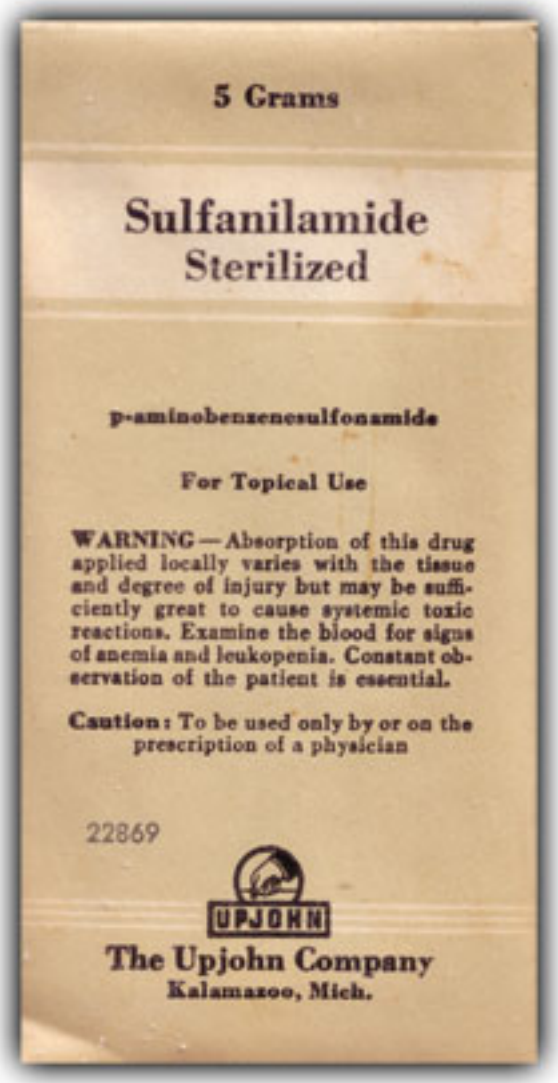
find one which would attack a germ but not the tissues.

Ehrlich decided to apply his theory to African sleeping-sickness, which is

Production of sulfa drugs

- Pharmaceutical companies started mass production
- US production of sulfa drugs was 350,000 pounds in 1937, doubled by 1940, and by 1942, was 10 million pounds
- Until 1938, available without a prescription
- Inexpensive
- Ongoing research to synthesize other sulfa compounds – by early 1940s, there were 5000 sulfa compounds synthesized


THIS ENVELOPE CONTAINS STERILE
SHAKER PACKAGE OF 5 GRAMS
CRYSTALLINE
SULFANILAMIDE, H.W.&D.
(p-aminobenzenesulfonamide)
H.W. & D.
For external use only
in case of wounds.
DIRECTIONS:
Sprinkle evenly over
wound before apply-
ing First Aid dressing.
HYNSON, WESTCOTT & DUNNING
INCORPORATED
BALTIMORE, MARYLAND


5 Grams
Sulfanilamide
Sterilized
p-aminobenzenesulfonamide
For Topical Use
WARNING — Absorption of this drug applied locally varies with the tissue and degree of injury but may be sufficiently great to cause systemic toxic reactions. Examine the blood for signs of anemia and leukopenia. Constant observation of the patient is essential.
Caution: To be used only by or on the prescription of a physician
22869
UPJOHN
The Upjohn Company
Kalamazoo, Mich.

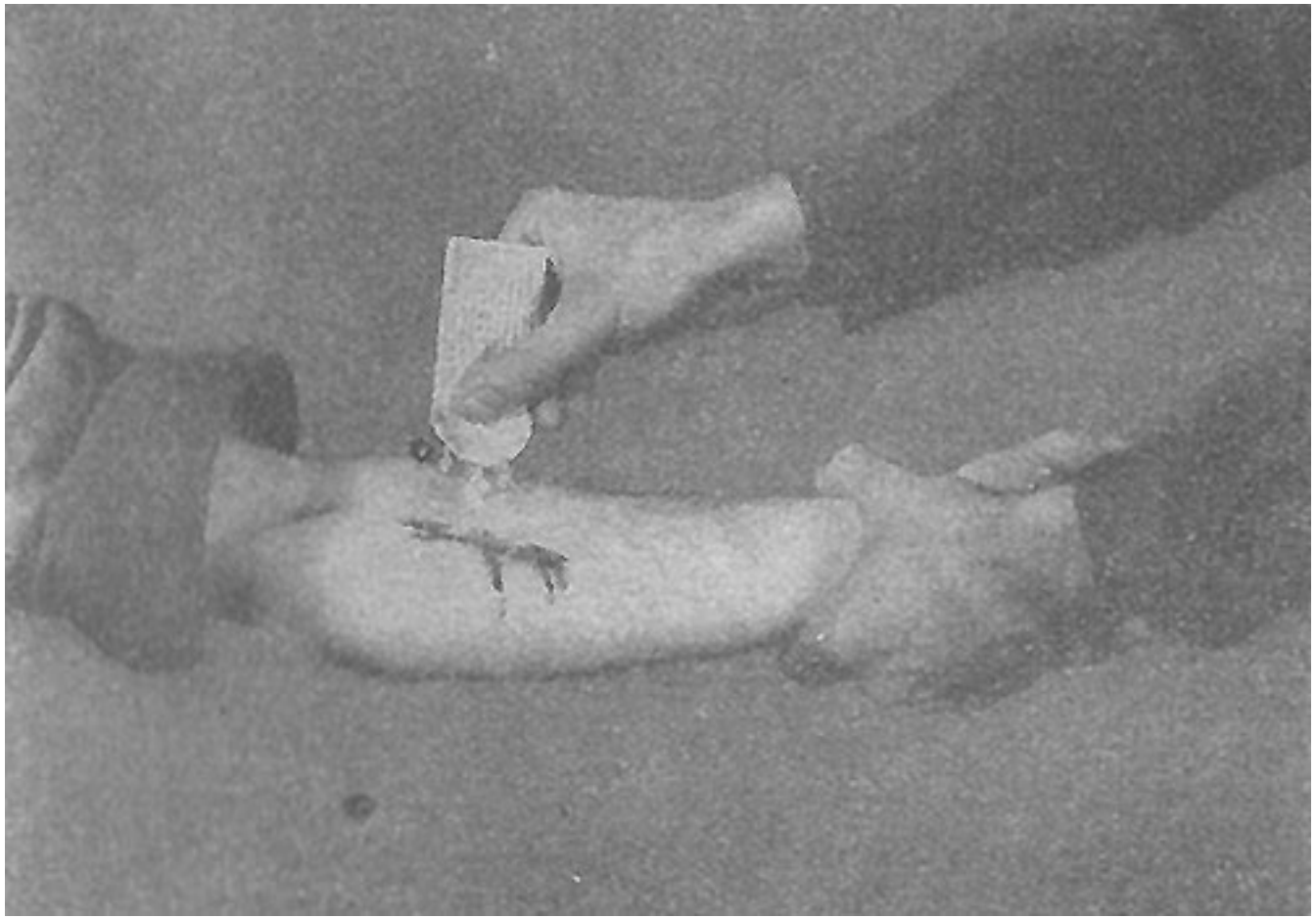
Historical importance of sulfa drugs

- Reduced infectious-disease mortality (this paper)
- First success of modern chemical pharmacology
- Widely used in WWII
- Prompted creation of the Food and Drug Administration

Sulfa drugs in WWII

Sulfa drugs in WWII

- U.S. soldiers were issued a first aid pouch with a packet of sulfa powder
- Instructed to immediately sprinkle sulfa powder on any open wound to prevent infection
- Medics also carried sulfa tablets
- Important in treating dysentary




WOUND
TABLETS
THE UPJOHN COMPANY
WOUND
TABLETS
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THE UPJOHN COMPANY
KALAMAZOO, MICH.
IF HIT IN BELLY
IF HIT IN BELLY
IF HIT IN BELLY
THE UPJOHN COMPANY

Elixir of Sulfanilamide

Elixir of Sulfanilamide

- In 1937, 108 people died from consuming the "Elixir of Sulfanilamide," an untested liquid sulfa product
- Chemical that the sulfa compound was mixed with was poisonous (liver and kidney failure)
- Incident prompted passage of 1938 Federal Food, Drug, and Cosmetic Act
  - Mandated safety testing of drugs
  - Prohibited sale of some non-narcotic drugs without a prescription
- Sulfapyridine was the first drug reviewed under the FDC Act
- Prompted creation of the FDA

Outline of rest of talk

- Data
- Trend breaks
- Regression analysis
- Urban-rural differences
- Black-white differences

Data

- Vital statistics data for the U.S., at the national-, state-, and city-level for the period from 1920 to 1950
- Maternal mortality, pneumonia, scarlet fever, and meningitis ("treated" diseases)
- Comparison diseases: tuberculosis, chronic diseases
- City-level data on maternal mortality, 1928 to 1940 for 329 cities with an initial population $>$250,000

Summary statistics

Table 1: National and state-level mortality statistics (deaths per 100,000)

	Panel A: National mortality rates				Panel B: Ave. state mortality rate	
	1920	1950	1925 to 1936 Mean	1937 to 1943 Mean	1925 to 1936 Mean	1937 to 1943 Mean
All-cause mortality	1424	842	1245	1065		
Treated diseases						
MMR	800	75	641	345	653	361
Flu/pneumonia	213	26	122	75	118	79
Scarlet Fever	3.0	0.02	1.9	0.6	2.2	0.7
Control diseases						
TB	119	22	72	47	70	46
Chronic diseases						
Diabetes	20	14	23	25	19	23
Heart disease	204	308	255	286	205	264
Cancer	105	125	115	119	95	110
No. of states					*39 -48*	*48*

Summary statistics by race

Table 1 continued: By race (deaths per 100,000)

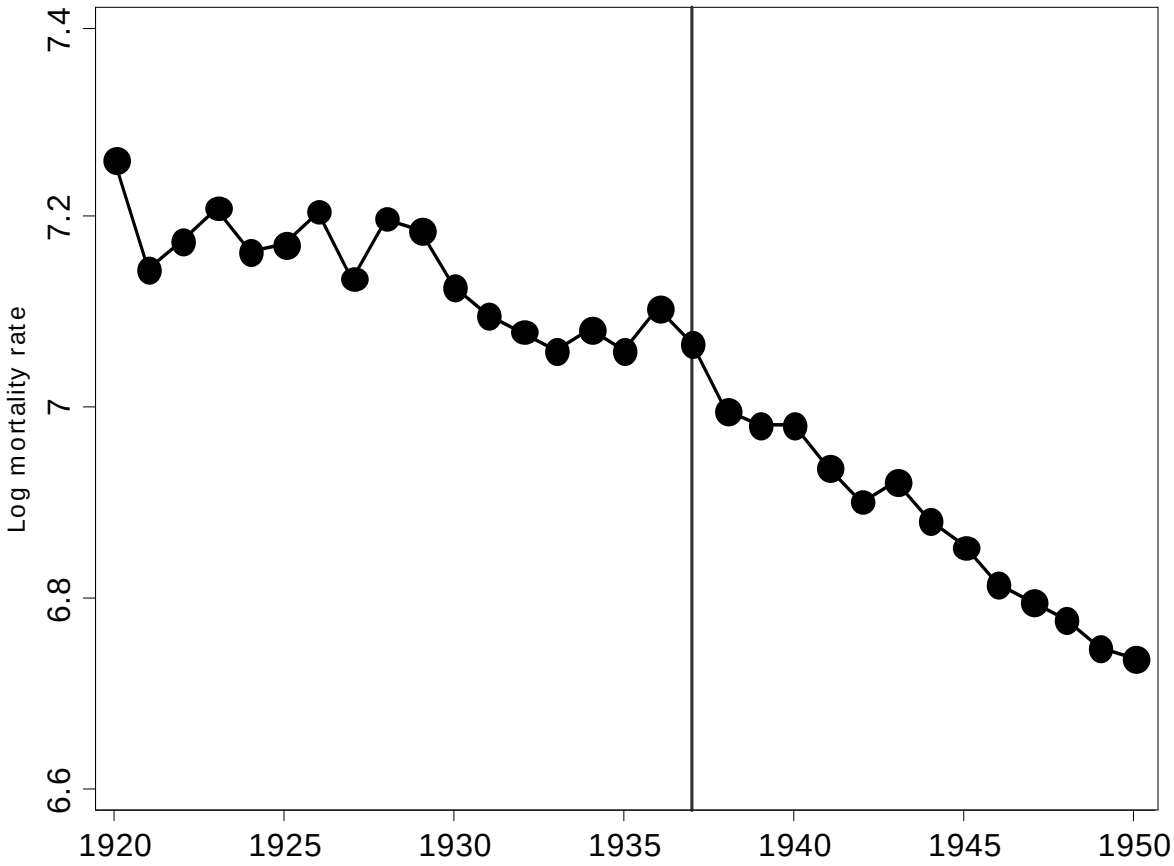
	Panel A: National mortality rates				Panel B: Ave. state mortality rate	
	1920	1950	1925 to 1936 Mean	1937 to 1943 Mean	1925 to 1936 Mean	1937 to 1943 Mean
By race						
MMR - White	760	61	585	312	644	358
MMR - Black	1281	222	1068	711	1095	739
Flu/pneumonia - White	204	23	112	67	115	75
Flu/pneumonia - Black	319	57	219	144	205	141
Scarlet Fever - White	3.4	0.02	2.0	0.7	1.7	0.5
Scarlet Fever - Black	0.5	0.02	0.5	0.2	0.5	0.3
TB - White	105	17	59	37	55	38
TB - Black	274	68	195	133	176	125
No. of states	*na*	*na*	*na*	*na*	*14-18*	*18*

Testing for and quantifying the effects of sulfa drugs

- More inferential then many empirical analyses
- Graphical analysis
- Trend break analysis: Do mortality time series have trend breaks when sulfa drugs were introduced?
- Regression analysis: Quantify effects of sulfa drugs by attributing to sulfa drugs post-1937 declines in mortality for treated diseases

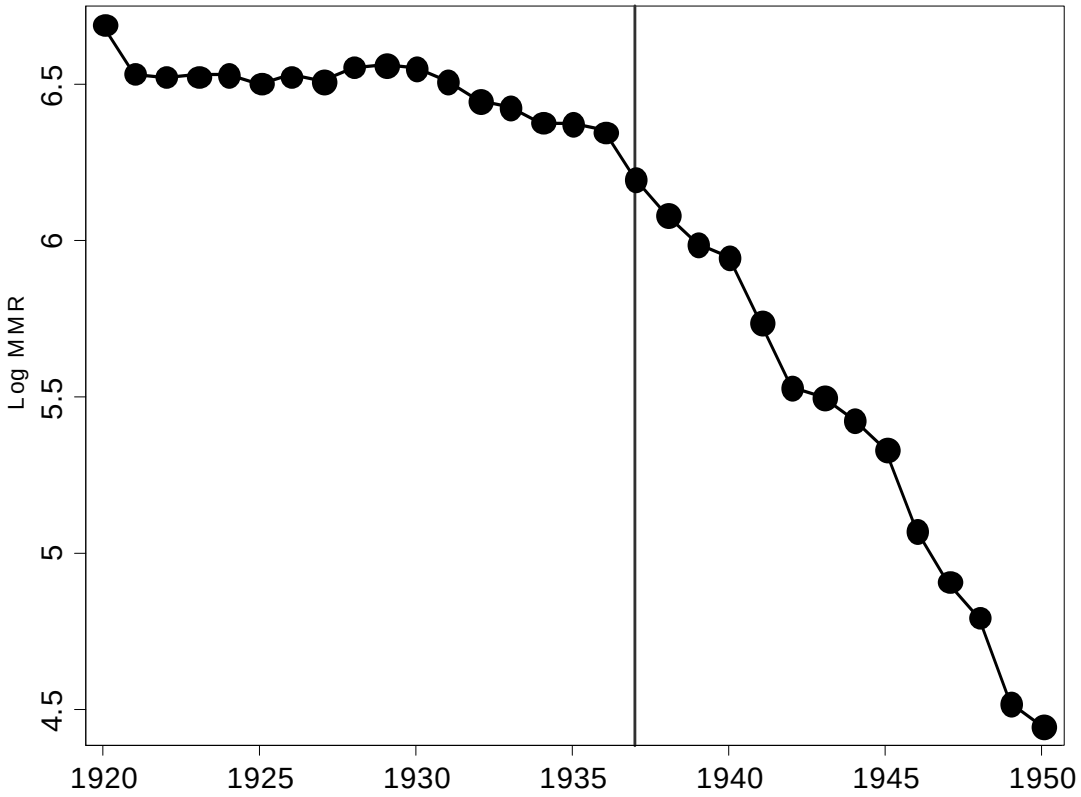
All-cause mortality

Figure 1: Total mortality rate per 100,000 (in logs), 1920 – 1950



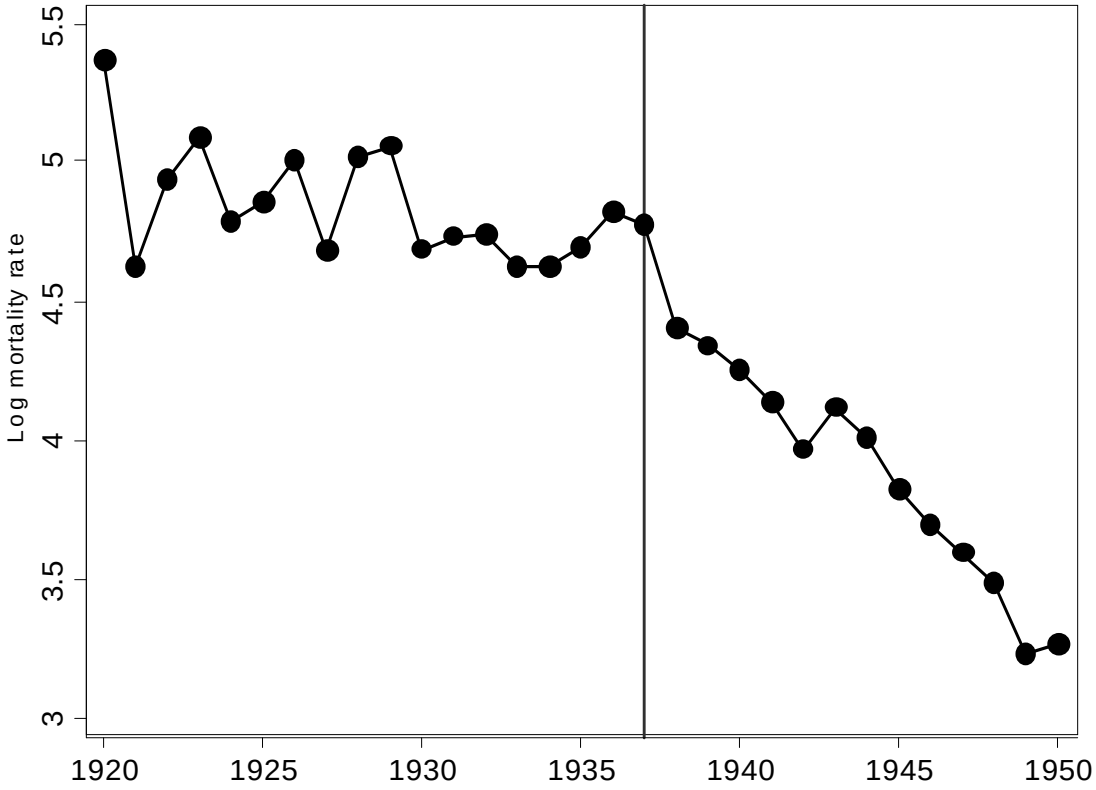
Maternal mortality ratio

a. Log maternal mortality ratio (deaths per 100,000 live births)



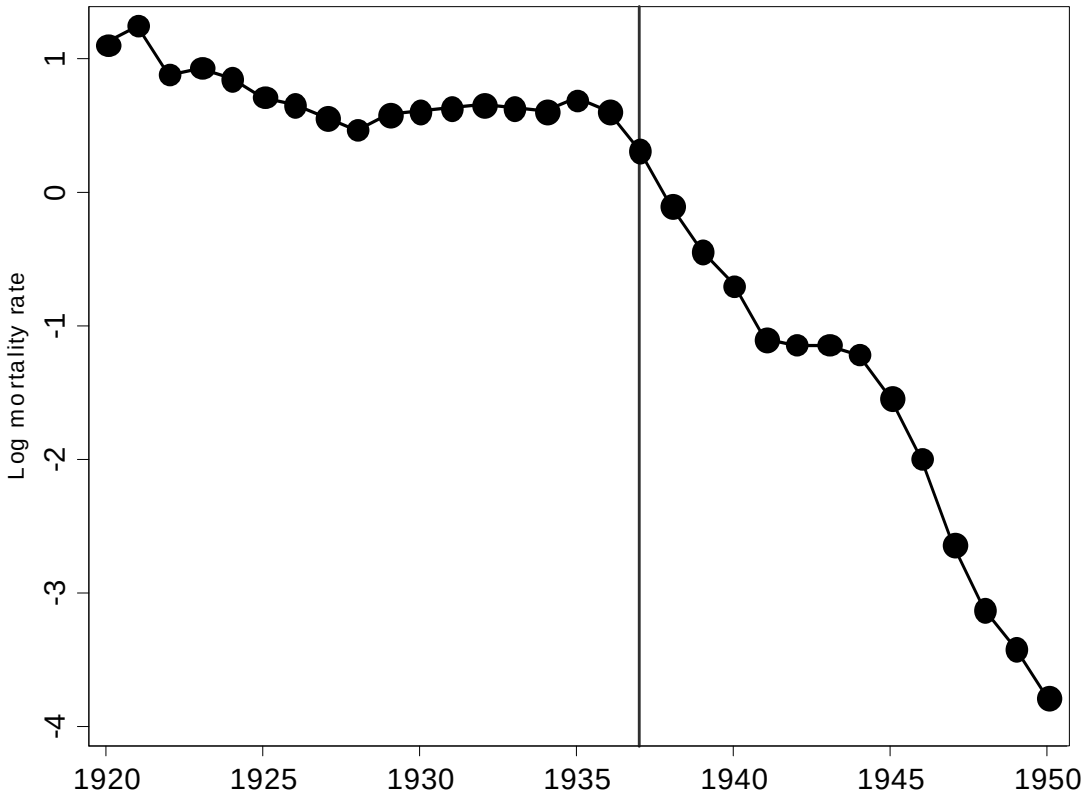
Pneumonia and influenza

b. Log influenza and pneumonia mortality rate per 100,000



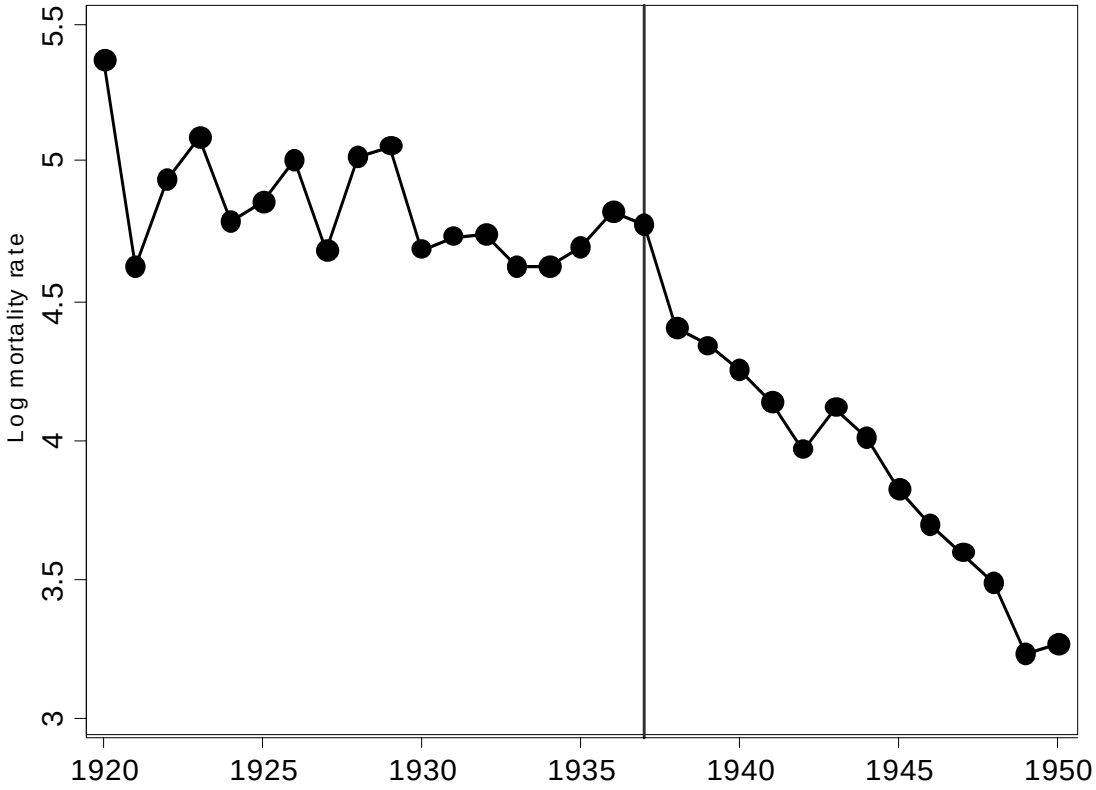
Scarlet fever

c. Log scarlet fever mortality rate per 100,000

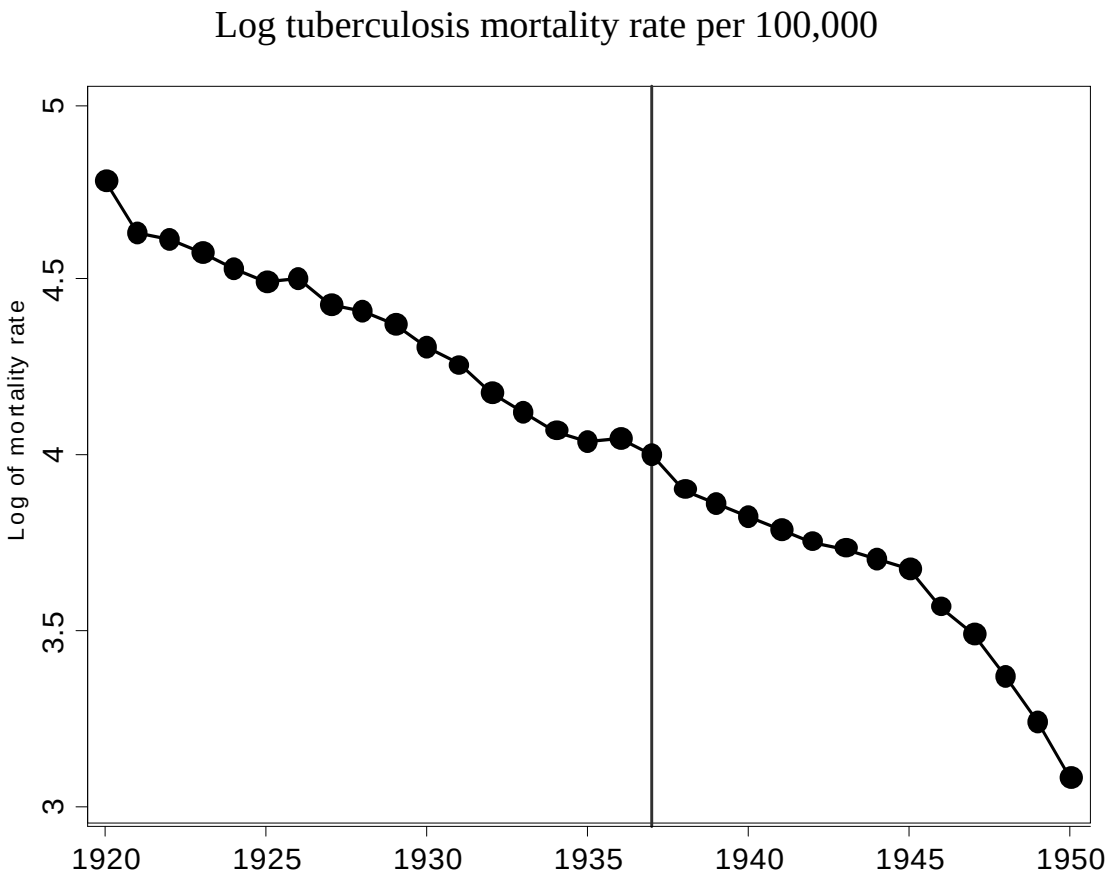


Meningitis

b. Log influenza and pneumonia mortality rate per 100,000

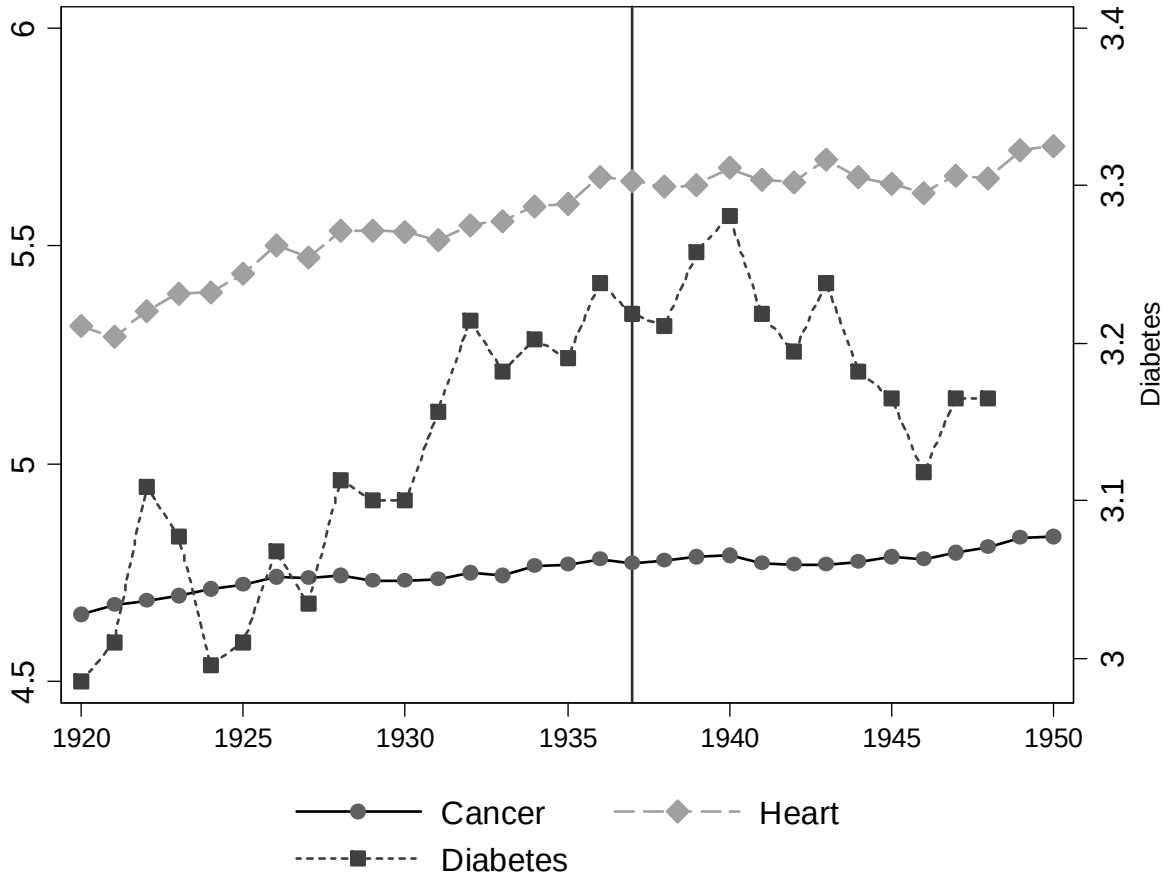


Tuberculosis (unaffected by sulfa drugs)



Chronic diseases (unaffected by sulfa drugs)

Log mortality rate (per 100,000) for cancer, diabetes, and heart disease



Trend break analysis

- Estimate following model

$$\log M_t \log M_{t-1} = \alpha + \delta D_t(\tau) + \varepsilon_t$$

- Dependent variable is first difference of log mortality
- $D_t(\tau)$ equals 0 before Year τ and equals 1 for subsequent years
- In using first differences, we are testing for a trend break rather than level change in mortality at year τ
- Estimate equation ten times, with τ taking on each value between 1933 and 1942
- For each estimate, test the null hypothesis of no trend break, or $\delta = 0 \Rightarrow$ Largest F-stat tells us the best possible break point and the statistical significance

Trend breaks in the mortality series

Table 2: Testing for year of trend break in national mortality series

	Break year	Test statistic
All-cause mortality	1937	2.97
Diseases treated with sulfa drugs		
MMR	1937***	29.23
Pneumonia/influenza	1938	3.09
Scarlet Fever	1937***	17.34
Control disease		
TB	1942	1.64

Regression analysis

- Test for changes in level of mortality in 1937:

$$\log M_t = \beta_0 + \beta_1 Year_t + \delta_0 Post1937_t + \varepsilon_t$$

- Test for changes in level of and trend in mortality in 1937:

$$\log M_t = \beta_0 + \beta_1 Year_t + \delta_0 Post1937_t + \delta_1 Post1937_t \times Year_t + \varepsilon_t$$

Change in mortality post-1937

Table 3: Effect of sulfa drugs using national-level time series by disease, 1925-1943

	All-cause		MMR		Pneumonia/influenza	
	(1)	(2)	(1)	(2)	(1)	(2)
Post-1937	-0.024	-0.007	-0.304**	-0.148***	-0.163	-0.037
	(0.023)	(0.019)	(0.140)	(0.032)	(0.122)	(0.076)
Year*Post-1937		-0.012**		-0.108***		-0.087***
		(0.005)		(0.009)		(0.026)
Observations	19	19	19	19	19	19

Change in mortality post-1937 (continued)

Table 3: Effect of sulfa drugs using national data (continued)

	Scarlet fever		TB	
	(1)	(2)	(1)	(2)
Post-1937	-0.862**	-0.495***	0.0151	0.006
	(0.364)	(0.104)	(0.025)	(0.022)
Year*Post-1937		-0.254***		0.0061
		(0.033)		(0.006)
Observations	19	19	19	19

Effect sizes

- Generally bigger effects with trend-break model
- Sulfa drugs caused overall mortality to fall by 2 to 3%
- Maternal mortality: 24 to 36%
- Pneumonia: 17 to 32%
- Scarlet fever: 52 to 65%
- Increased life expectancy at birth by 0.4 to 0.7 years
- Slight underestimate of mortality effects because of omitted causes of death
- Also large morbidity effects (e.g., gonorrhea)

Comparison to clinical trials

- Pneumonia
  - In clinical trials, sulfa drugs reduced mortality by 50 to 70%, compared to our 17 to 32% estimate
  - Larger effect in clinical trials is not surprising since only a portion of the population afflicted with pneumonia took sulfa drugs
  - Also, drugs are more efficacious in a controlled, clinical setting

Comparison to clinical trials

- Maternal mortality
  - Sulfa drugs reduced mortality from puerperal fever by 81% in clinical trials $\rightarrow$ 32% reduction in maternal mortality
  - We find a maternal mortality decline of 24 to 36%
  - Why such a large population effect? Majority of births were physician-assisted by the mid-1930s, so sulfa drugs were administered in a high proportion of puerperal fever cases in the general population
- No clinical trial data for scarlet fever

Using TB as control disease

Table 4: Effect of sulfa drugs on mortality for "treated" diseases, 1937 – 1943

Dependent variable = ln (mortality)	MMR		Pneumonia/influenza		Scarlet fever	
	(1)	(2)	(1)	(2)	(1)	(2)
Panel A: National-level data, all years, 1925-1943						
Treated*Post-1937	-0.319**	-0.163***	-0.178	-0.052	-0.877**	-0.510***
	(0.118)	(0.041)	(0.176)	(0.126)	(0.337)	(0.110)
Treated*Year*Post-1937		-0.108***		-0.087***		-0.254***
		(0.009)		(0.031)		(0.036)
Observations	38	38	38	38	38	38
R-squared	0.99	1.00	0.91	0.95	0.99	1.00

Robustness to dropping 1935-37

Table 4: Effect of sulfa drugs on mortality for "treated" diseases, 1937 – 1943

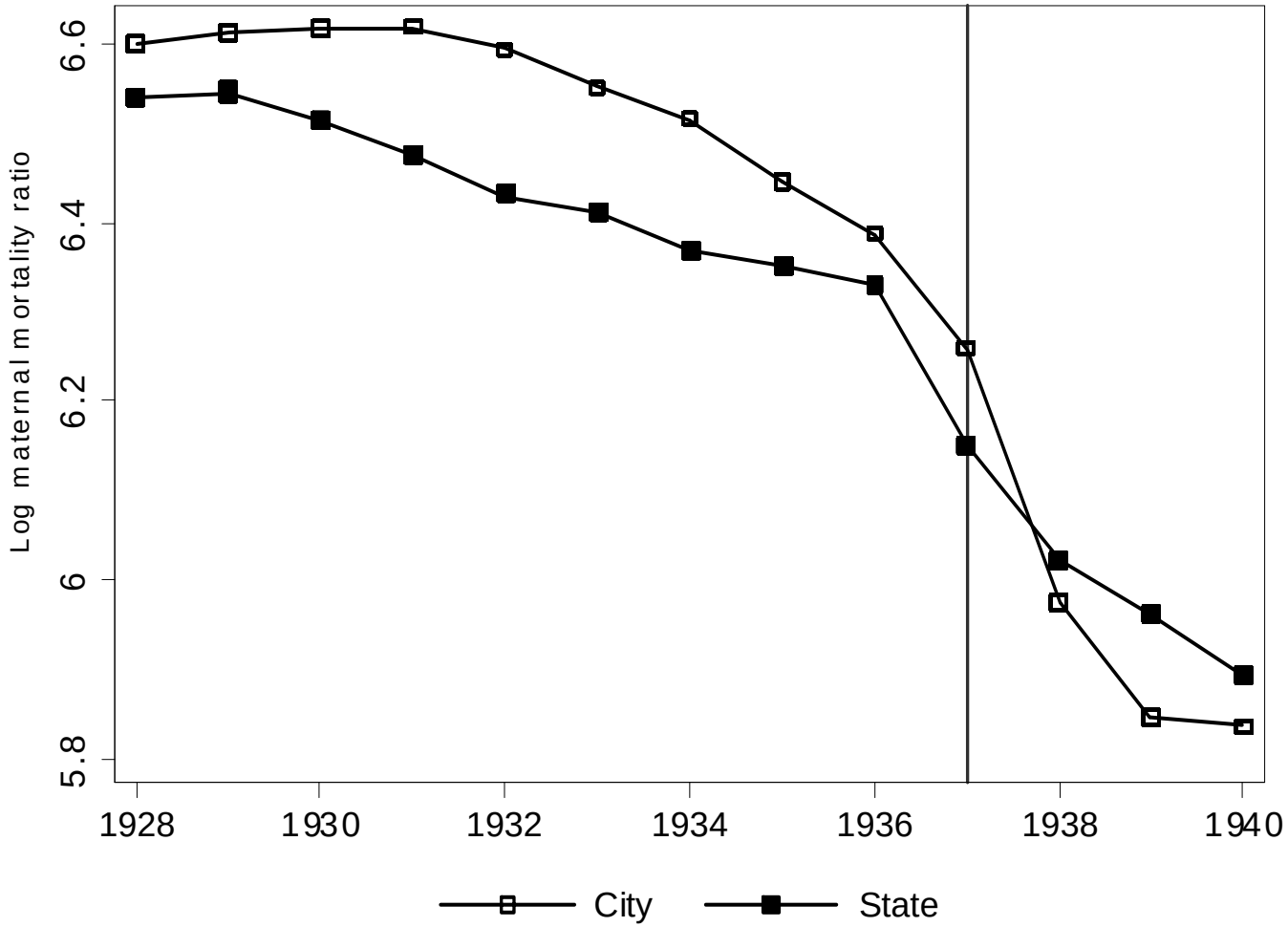
Dependent variable = ln (mortality)	MMR		Pneumonia/influenza		Scarlet fever	
	(1)	(2)	(1)	(2)	(1)	(2)
Panel C: State-level, excluding 1935 to 1937						
Treated*Post-1937	-0.288**	-0.125**	-0.072	-0.026	-0.714***	-0.511***
	(0.134)	(0.054)	(0.093)	(0.084)	(0.254)	(0.128)
Treated*Year*Post-1937		-0.117***		-0.033		-0.146***
		(0.013)		(0.025)		(0.037)
Observations	1448	1448	1448	1448	1432	1432
R-sq.	0.999	0.999	0.841	0.847	0.946	0.950

Sulfa drugs diffused to cities first

- Diffused first in cities with major teaching hospitals
- Diffused next to other cities
- Did mortality for sulfa-treatable diseases fall more for cities over this period?
- We do not have rural data
- Instead, compare mortality in cities in a given state to mortality in the whole state (aggregate of cities, towns and rural areas)
- Expect bigger declines in the cities than for the state

MMR — urban/rural differences

Figure 5: City and state trends in MMR (in logs), 1928 – 1940



Urban-rural differences

Table 5: Urban-state differences in the effect of sulfa drugs on MMR

Dependent variable=ln(MMR)	(1)	(2)
Panel A: All years, 1928-1940		
Urban*Post-1937	-0.137***	-0.098*
	(0.046)	(0.053)
Urban*Year*Post-1937		-0.059***
		(0.022)
Observations	4552	4552
R-squared	0.401	0.427

Racial differences in medical access

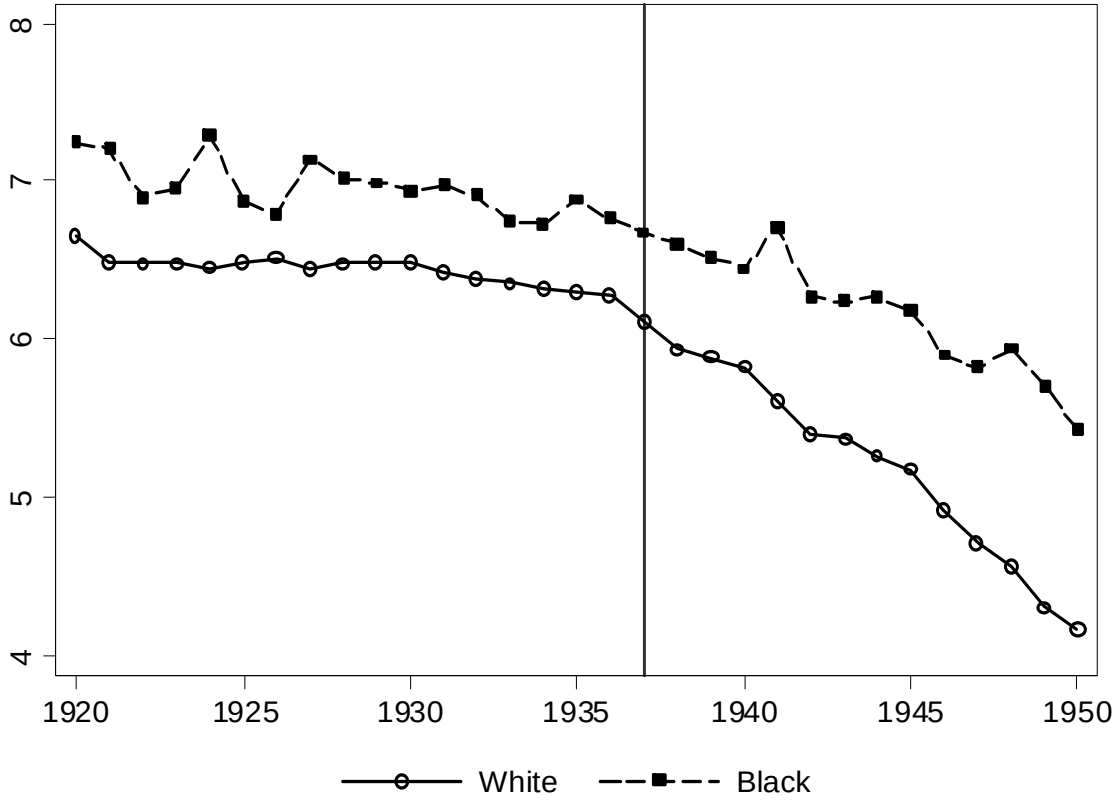
- Higher SES groups might use their greater resources to improve their health
- New medical technologies may increase inequalities in health because they tend to favor, at least initially, the better off

Racial differences in access to sulfa drugs

- Most blacks lived in lower-income South and in rural areas, often at far distances from hospitals and physicians
- Hospital segregation + greater resources in white facilities
- Home deliveries by untrained midwives much higher among black women in this period

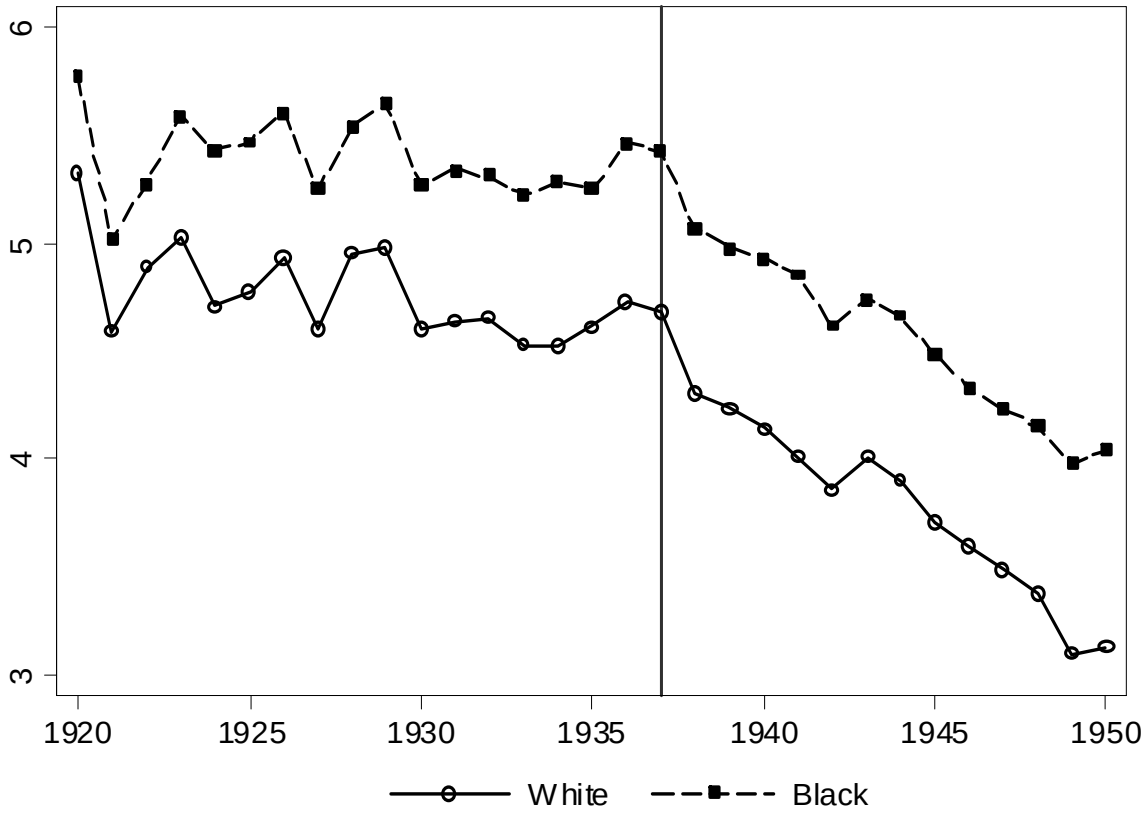
MMR by race

a: Log maternal mortality ratio, by race



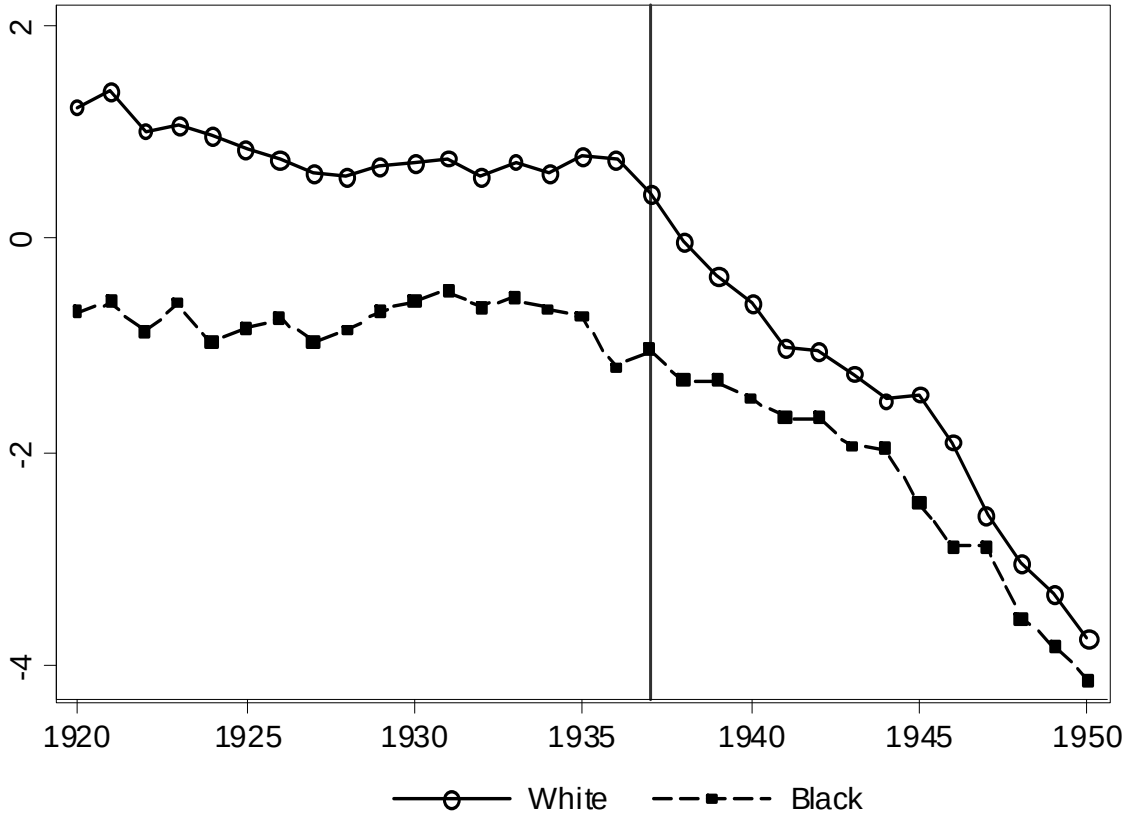
Pneumonia/influenza by race

b: Log influenza and pneumonia mortality rate, by race



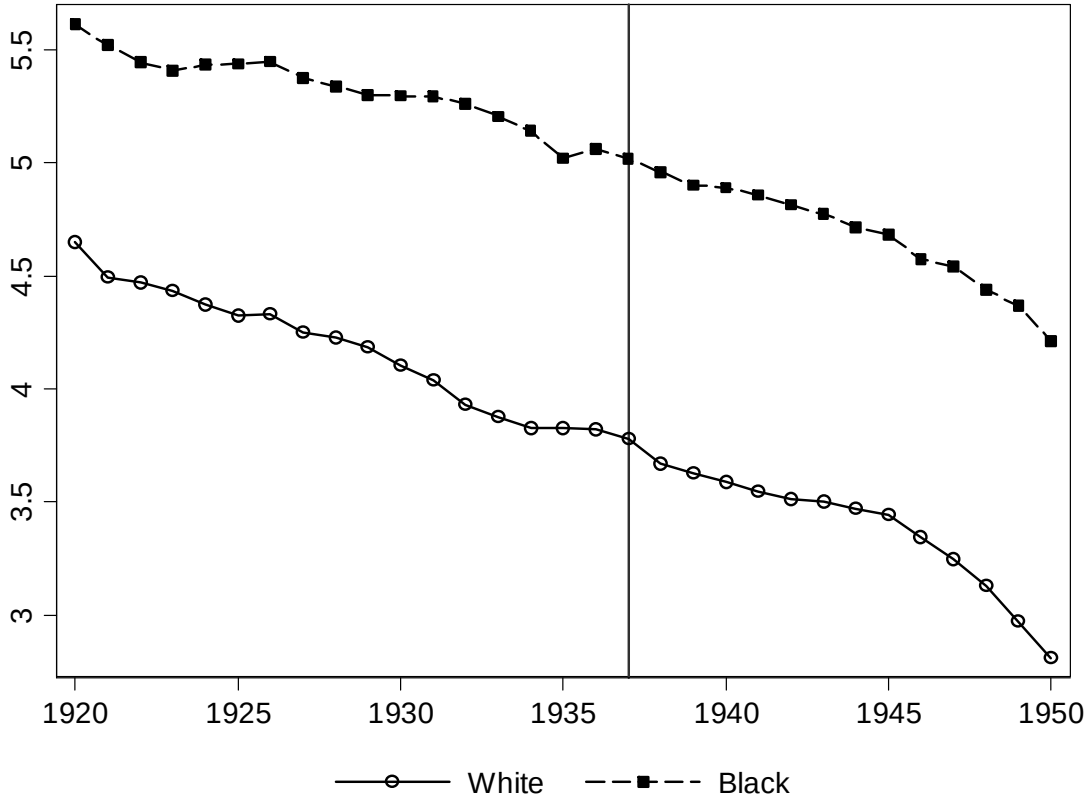
Scarlet fever by race

c: Log scarlet fever mortality rate, by race



Tuberculosis by race

d: Log tuberculosis mortality rate, by race



Results separately by race

Table 6: Racial differences in the effect of sulfa drugs on mortality, 1937-1943

	MMR		Pneumonia/influenza		Scarlet fever	
	(1)	(2)	(1)	(2)	(1)	(2)
Panel A: Whites						
Treated*Post-1937	-0.301**	-0.169***	-0.230	-0.104	-0.804***	-0.582***
	(0.115)	(0.044)	(0.183)	(0.122)	(0.221)	(0.164)
Treated*Year*Post-1937		-0.109***		-0.094***		-0.155***
		(0.010)		(0.027)		(0.032)
Obs.	644	644	652	652	539	539
R-sq.	0.967	0.972	0.856	0.883	0.976	0.981
Panel B: Blacks						
Treated*Post-1937	-0.133	-0.029	-0.115	-0.013	-0.134	-0.124
	(0.096)	(0.061)	(0.165)	(0.132)	(0.187)	(0.155)
Treated*Year*Post-1937		-0.081***		-0.076***		-0.032
		(0.013)		(0.027)		(0.032)
Obs.	644	644	652	652	500	500
R-sq.	0.935	0.942	0.788	0.826	0.983	0.984

Racial differences, interacted model

Table 6: Racial differences in the effect of sulfa drugs on mortality, 1937-1943

	MMR		Pneumonia/influenza		Scarlet fever	
	(1)	(2)	(1)	(2)	(1)	(2)
Panel C: Fully interacted model						
Treated*Post-1937*Black	0.168**	0.140**	0.115**	0.091**	0.671***	0.458***
	(0.068)	(0.052)	(0.052)	(0.043)	(0.211)	(0.157)
Treated*Year*Post-1937*Black		0.028***		0.018**		0.123**
		(0.010)		(0.009)		(0.048)
Obs.	1288	1288	1304	1304	1039	1039
R-sq.	0.961	0.966	0.918	0.933	0.981	0.983

Conclusion

- Increased life expectancy by 0.4 to 0.7 years — 8 to 14% of the total improvement in life expectancy for these years
- Sulfa drugs had a significant impact on longevity, but most of the longevity gains during this era were due to other (probably non-medical) factors
- Sulfa drugs benefitted whites more than blacks, increasing racial inequality in maternal and pneumonia mortality and almost eliminating the black advantage in scarlet fever
- Unlike most life-saving innovations, sulfa drugs were inexpensive — full course of medicine cost less than $100 (2009 dollars)