Modeling the Emergence of Multidrug Antibiotic Resistance

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Abstract

One of the most worrisome aspects of the worldwide growth of antibiotic resistance is the emergence of bacterial strains (or "clones") that are resistant to multiple classes of antibiotics. Such multidrug resistance has made some life-threatening diseases more difficult and more expensive to treat, and has contributed to an increase in mortality from formerly well-controlled diseases such as tuberculosis. It has also led to increasing reliance on the newest and most powerful antibiotics, sparking concerns that resistance will soon reduce their effectiveness as well, and eliminate all options for treatment in some cases.

We have previously presented a small system dynamics model, drawing upon a case study of pneumococcal resistance to the beta-lactams, that portrays the development of resistance within a bacterial population to a single class of antibiotics. This model is now extended to consider growth in resistance to two different classes of antibiotics, with special application to pneumococcal resistance to the beta-lactams and the macrolides.

The extended model shows how selective pressure from antibiotics may cause multidrug resistant clones to become dominant over both non-resistant and single-class resistant strains, even when the microbiological mechanisms of resistance for the two antibiotic classes are unrelated. The implications for policy are explored. In particular, how can the growth of two-class resistance best be reversed? Does it require very large reductions in the use of both contributing antibiotic classes, or is there a less difficult way?

Background on multidrug resistance (MDR)

- MDR makes infections more difficult and expensive to treat, and has emerged in the last two decades in a variety of pathogens, including:

  - *S. aureus*: many strains resistant to all antibiotics except expensive vancomycin

  - *M. tuberculosis*: some strains now evade all treatment

  - *N. gonorrhoeae*: treatment now limited to cephalosporins

  - *S. dysentaria*: some strains treatable only by expensive fluoroquinolones, often unavailable in developing countries

  - *E. faecalis*: some strains now evade all treatment

  - *E. coli*: MDR found in strains causing urinary tract infections

  - *P. aeruginosa*: some strains now evade all treatment

  - *S. pneumoniae*: some strains resistant to six different classes of antibiotics

Source: Levy 1998.

Background on multidrug resistance (MDR), continued

- MDR may result from mutations affecting single or multiple biochemical mechanisms

    - Single mechanism

        - Within a drug class (due to chemical relatedness)

            - ex. altered penicillin-binding proteins (PBPs) affect all beta-lactam drugs (penicillins, cephalosporins, carbapenems)

        - Across multiple drug classes (due to target overlap or active efflux)

            - ex. one altered ribosomal enzyme confers common resistance to macrolides, lincosamides, and streptogramins ("MLS resistance")

    - Multiple mechanisms

        - Each mechanism confers resistance to a corresponding drug class

        - Multiple resistance genes often physically adjacent and transferred together in chromosomal "cassettes" or "integrons"

        - Multiply-resistant bacterial clones may gain reproductive advantage when multiple drug classes are used excessively

MDR in *S. pneumoniae* (**Pneumococcus**)
Data from the USA and Spain

Resistance number*	USA 1995/8 N	%	Spain 1990-6 N	%
0	2183	69.8%	3703	40.1%
1	293	9.4%	1732	18.7%
2	252	8.1%	840	9.1%
3	164	5.2%	1817	19.7%
4	122	3.9%	1151	12.5%
5	114	3.6%	N/A	N/A
All	3128	100.0%	9243	100.0%
1 or more	945	30.2%	5540	59.9%
2 or more	652	20.8%	3808	41.2%

* Resistance number: Number of specified drugs to which an isolate is resistant (includes both intermediately and highly resistant isolates.)
For USA, the five drugs include: penicillin, erythromycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP/SMP).
For Spain, the first four of these drugs are reported but not TMP/SMP.

Sources:
USA: Doern 1996 (N=1527 in 1995 sample), Doern 1999 (N=1601 in 1998 sample);
Spain: Fenoll et al. 1998 (continuous sampling 1990-1996).

Where we started: Modeling resistance to one drug class

- ## Initial focus on pneumococcal resistance to penicillin (PRP) and other beta-lactams

    - ### Three-state model is a simplification of the *near-continuum* of resistance states in PRP

        - Extensive use of beta-lactams has given mutant resistant pneumococci a reproductive advantage they would not otherwise have

        - The one-class model can reproduce historical PRP growth in USA, Spain, South Africa, and Hungary

        - See Homer et al., *System Dynamics Review* 16(4), 2000.

- ## Subsequent focus on pneumococcal resistance to erythromycin (PRE) and other macrolides

    - ### Two-state model reflects *essentially binary* situation in PRE

        - PRE emerged more recently than PRP, but has caught up in western countries, as macrolide use grew while beta-lactam use declined

        - The one-class model can reproduce historical PRE growth in USA, Spain, France, and Hungary

One-class resistance model used for studying PRP and PRE*

Multidrug Antibiotic Resistance - J. Homer et al.
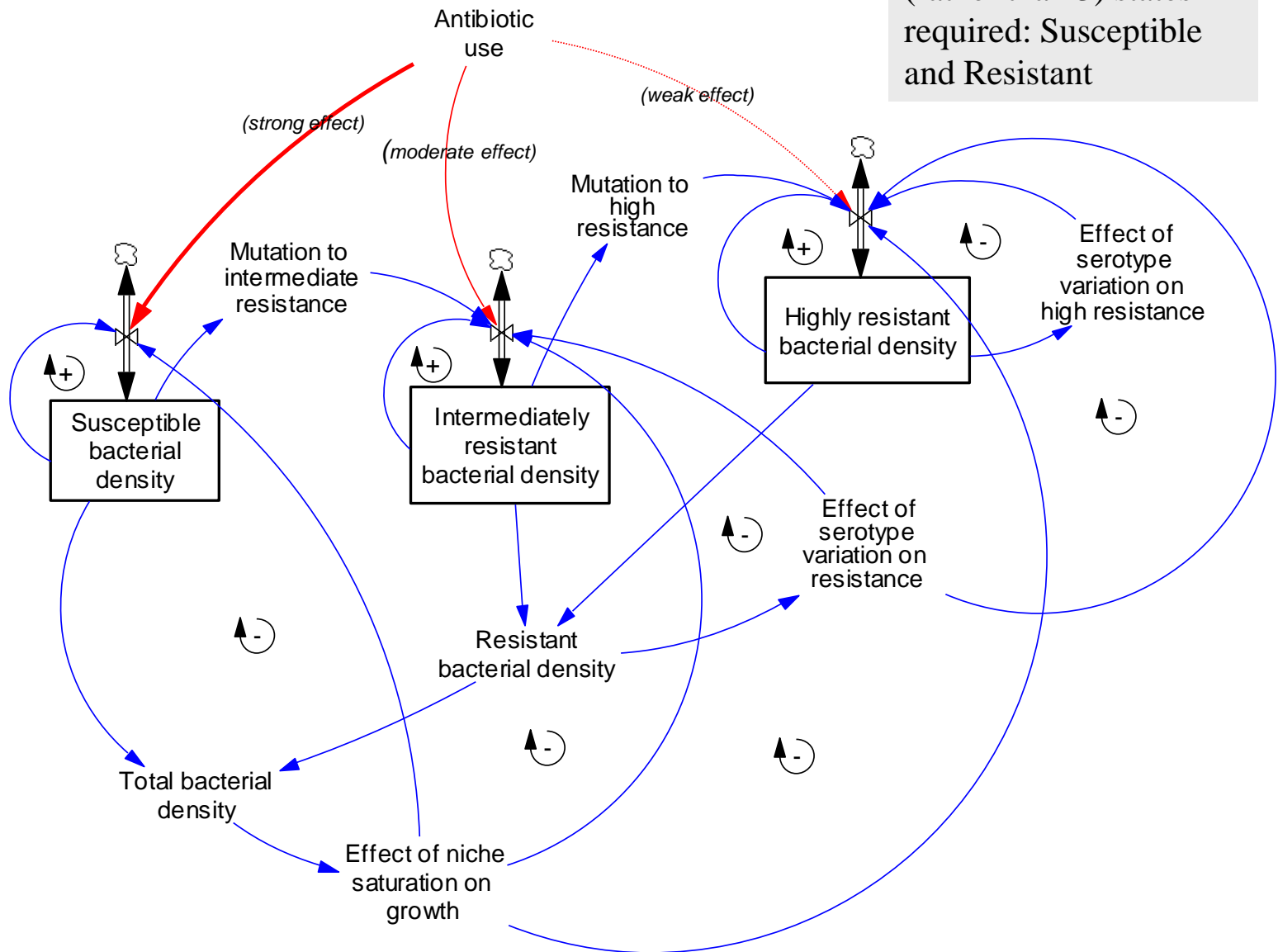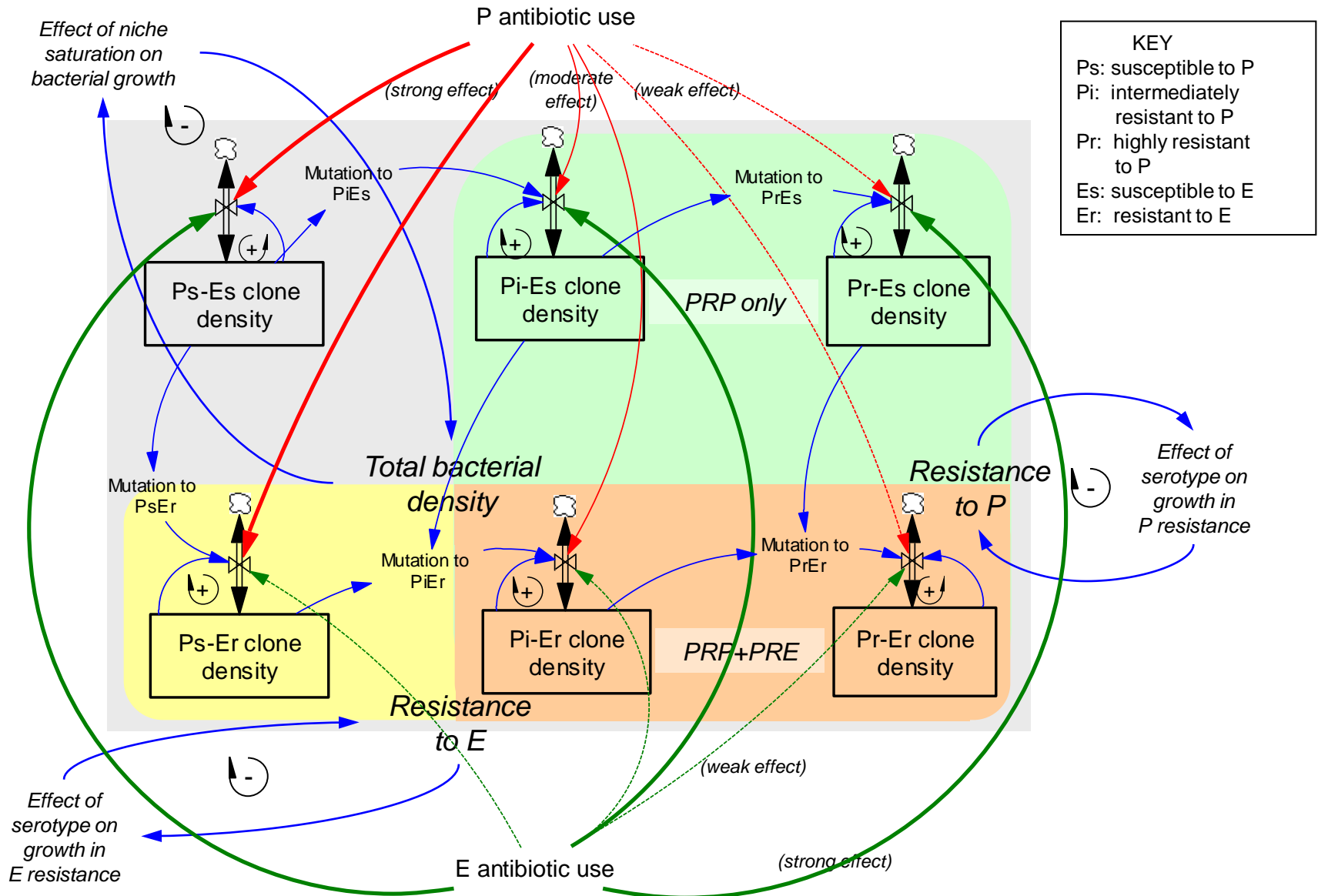
Modeling two-class resistance

- ## Purpose: To investigate how MDR clones may become dominant even when resistance mechanisms differ

  - To avoid undue complexity, modeled co-resistance to two drug classes only; anticipated that lessons learned for two-class MDR would apply to higher-order MDR as well

  - To represent PRP/PRE co-resistance, need 6 clone types

    – 3 PRP resistance states x 2 PRE resistance states

  - Initial version of MDR model assumed largely *independent* transfer of PRP and PRE genes

    – This model able to show how two-class resistant clones may develop from single-class resistant clones, through change in a single gene; but *unable* to show emerging dominance of these new MDR clones

  - Subsequent version assumes mostly *co-transfer* of PRP and PRE genes

    – This model able to show emerging MDR clone dominance given sufficient use of both drug classes

Two-class resistance model used for studying PRP/PRE
## (P: penicillin/beta-lactams; E: erythromycin/macrolides)

Multidrug Antibiotic Resistance - J. Homer et al.

Pneumococcal resistance to penicillin (PRP): One- and two-class model simulations vs. history

PRP here includes both intermediate (MIC≥0.12 µg/mL) and high resistance (MIC≥2 µg/mL) in isolates from normally sterile sites.
MIC: Minimum inhibitory concentration
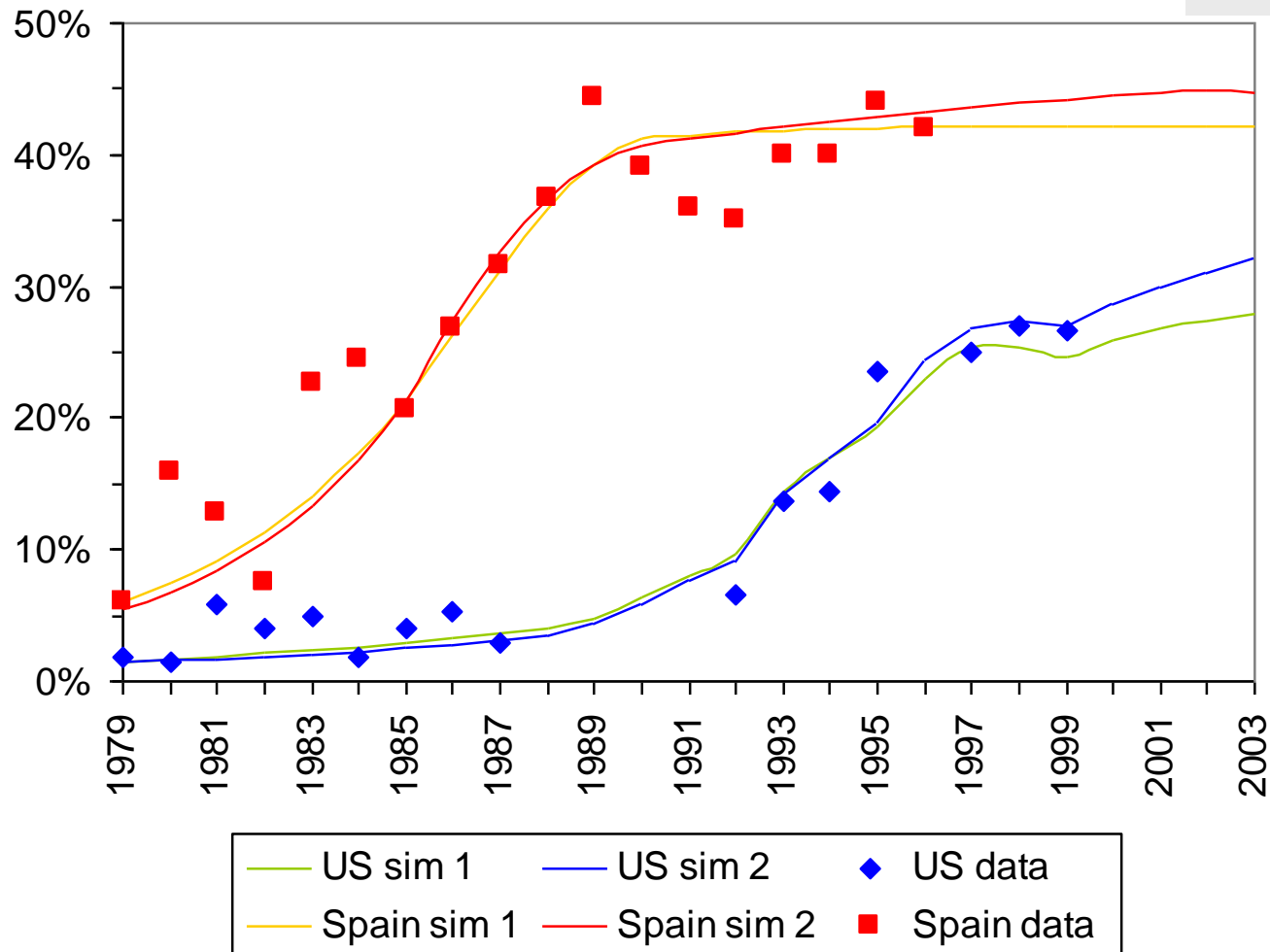
Sources: <u>USA</u>: Breiman 1994, Butler 1996, Doern 1996, Doern 1999, CDC 1999; <u>Spain</u>: Fenoll 1991, Fenoll 1998.

Beta-lactam use data and assumptions
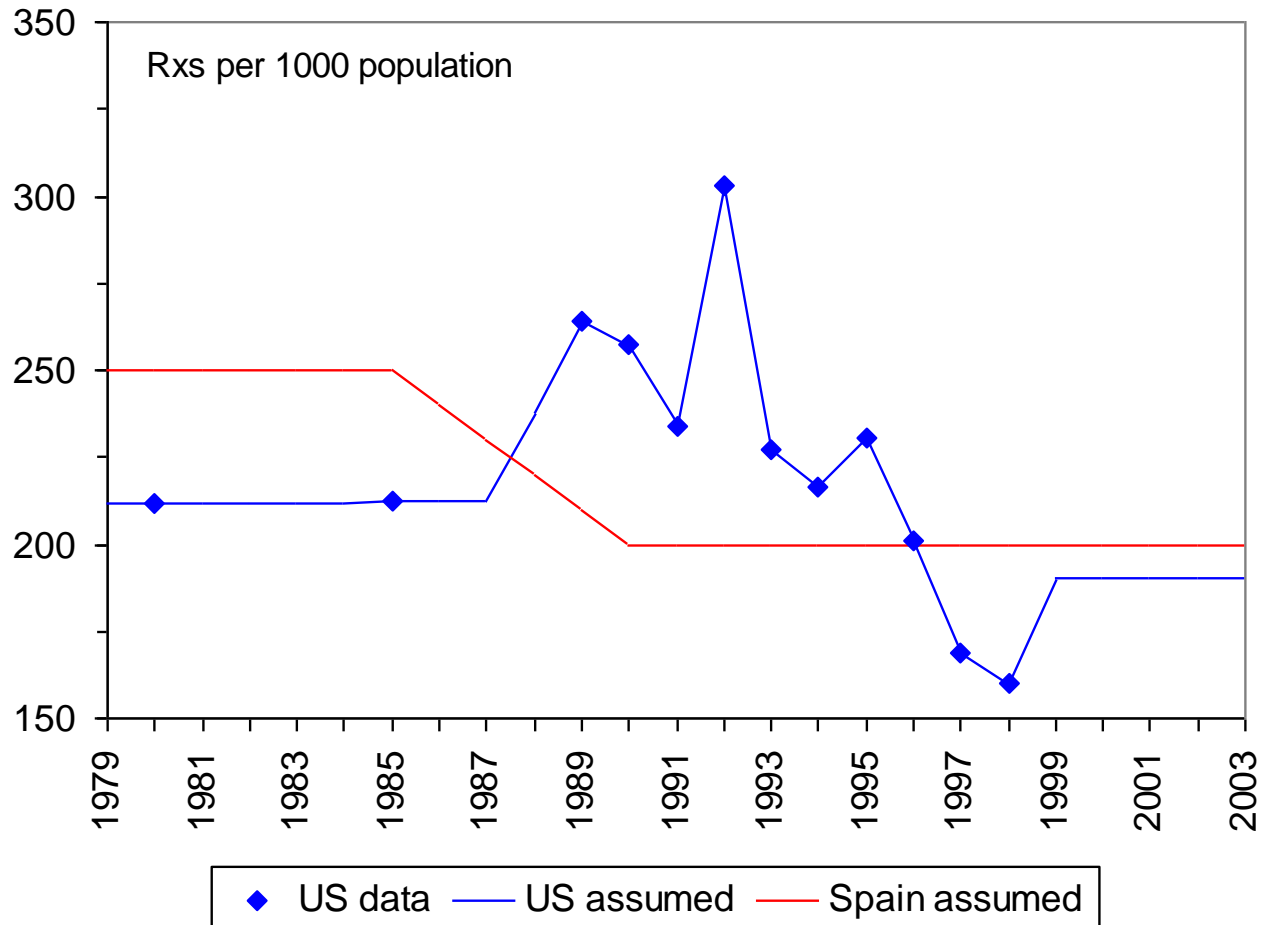
Sources (USA): McCaig and Hughes 1995, NCHS 1998.

Multidrug Antibiotic Resistance - J. Homer et al.

Pneumococcal resistance to erythromycin (PRE): One- and two-class model simulations vs. history

Sources: <u>USA</u>: Breiman 1994, Butler 1996, CDC 1999; <u>Spain</u>: Fenoll 1991, Fenoll 1998.

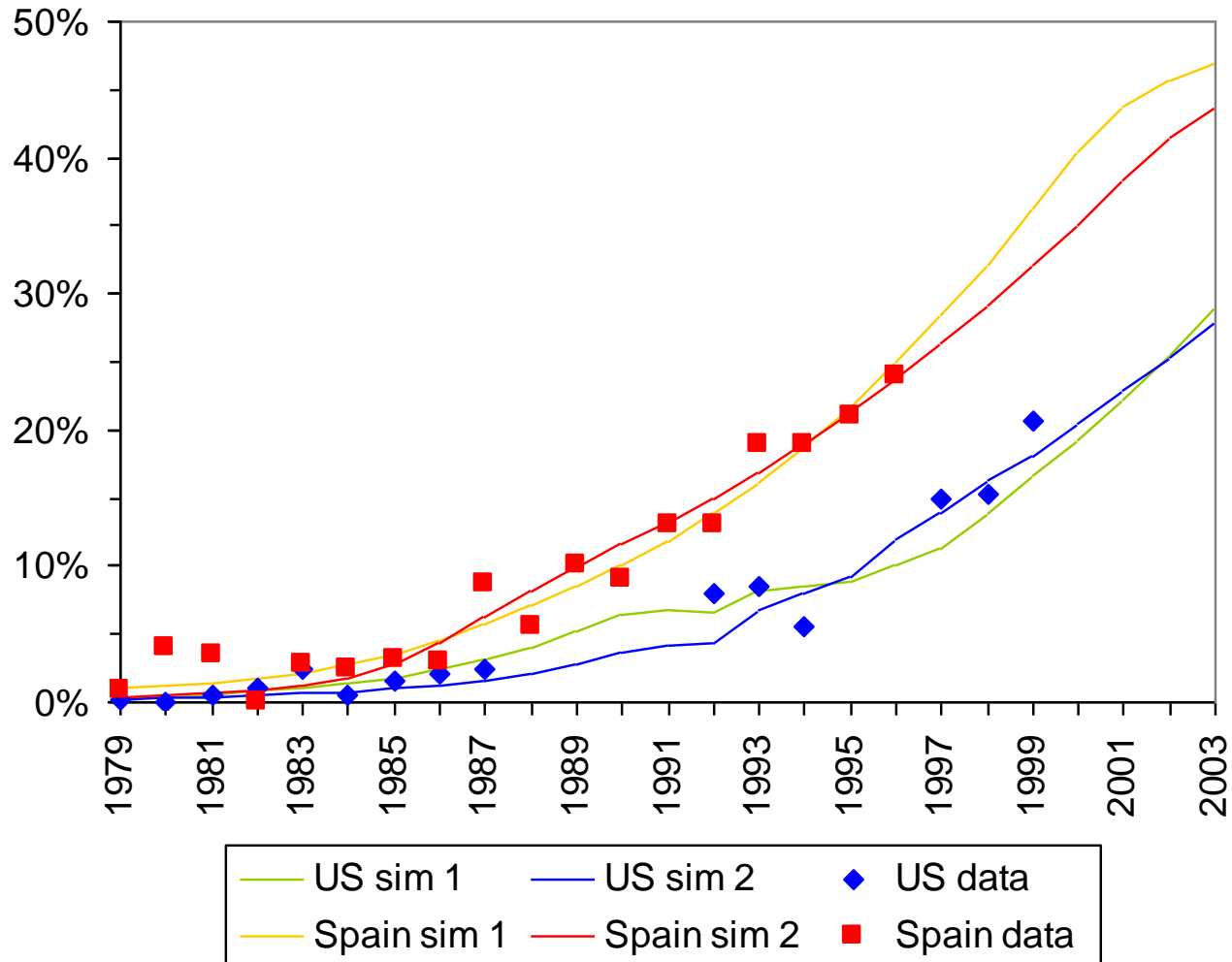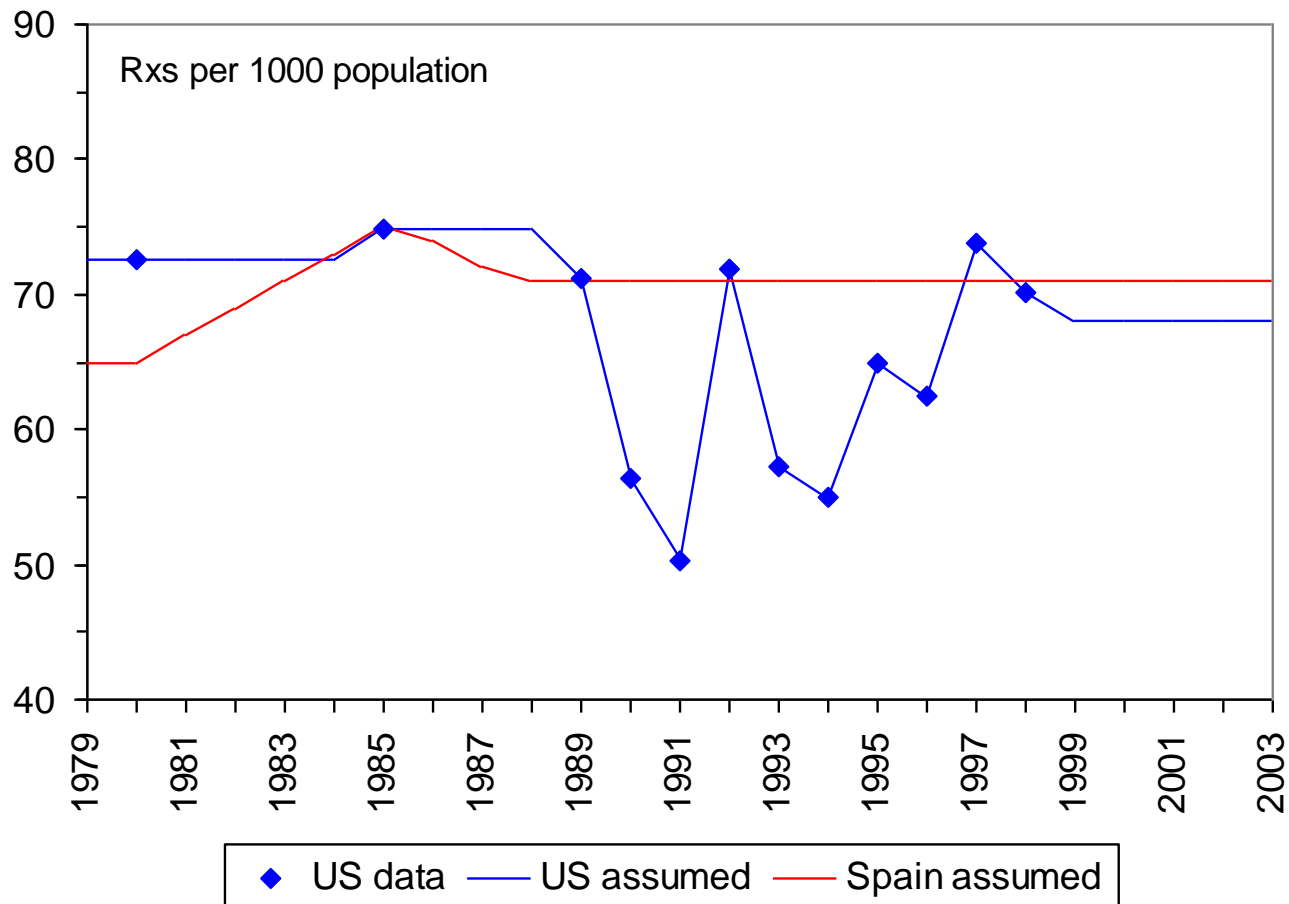# Macrolide use data and assumptions

Sources (USA): McCaig and Hughes 1995, NCHS 1998.

Key parameter values in one-class and two-class models

Relative reproductive fitness [f]

	One-class	Two-class*
f(Ps)	1	1
f(Pi)	0.942	0.942
f(Pr)	0.936	0.936
f(Es)	1	1
f(Er)	0.942	0.942

Antibiotic inhibition factors [b]*

	One-class	Two-class
b(Ps)	0.09	0.09
b(Pi)	0.03	0.03
b(Pr)	0.0040	0.0055
b(Es)	0.09	0.09
b(Er)	0.0150	0.0165

* In the two-class model, relative reproductive fitness of a clone type is found by multiplying the f-values of its component P and E genes; ex., f(PrEr) = f(Pr)f(Er) = (.936)(.942) = .8817.

** These b factors describe inhibition effect at a normalizing level of antibiotic use (ABn), expressed in prescriptions per thousand population per year. For beta-lactams (BL), ABn = 200; for macrolides (M), ABn = 70. Given these normalizing levels, the effect of BL use on proliferation = $(1-b)^{BL/200}$; the effect of M use on proliferation = $(1-b)^{M/70}$.

In the two-class model, the effect of antibiotic use on proliferation of a clone type is found by multiplying the beta-lactam and macrolide effects on its component P and E genes; ex., the effect of antibiotic use on proliferation of PrEr = $(1 - 0.0055)^{BL/200}(1 - 0.0165)^{M/70}$.

Initial (1979) values in one-class and two-class models

Resistance percentages, initial (1979)

Resistance types
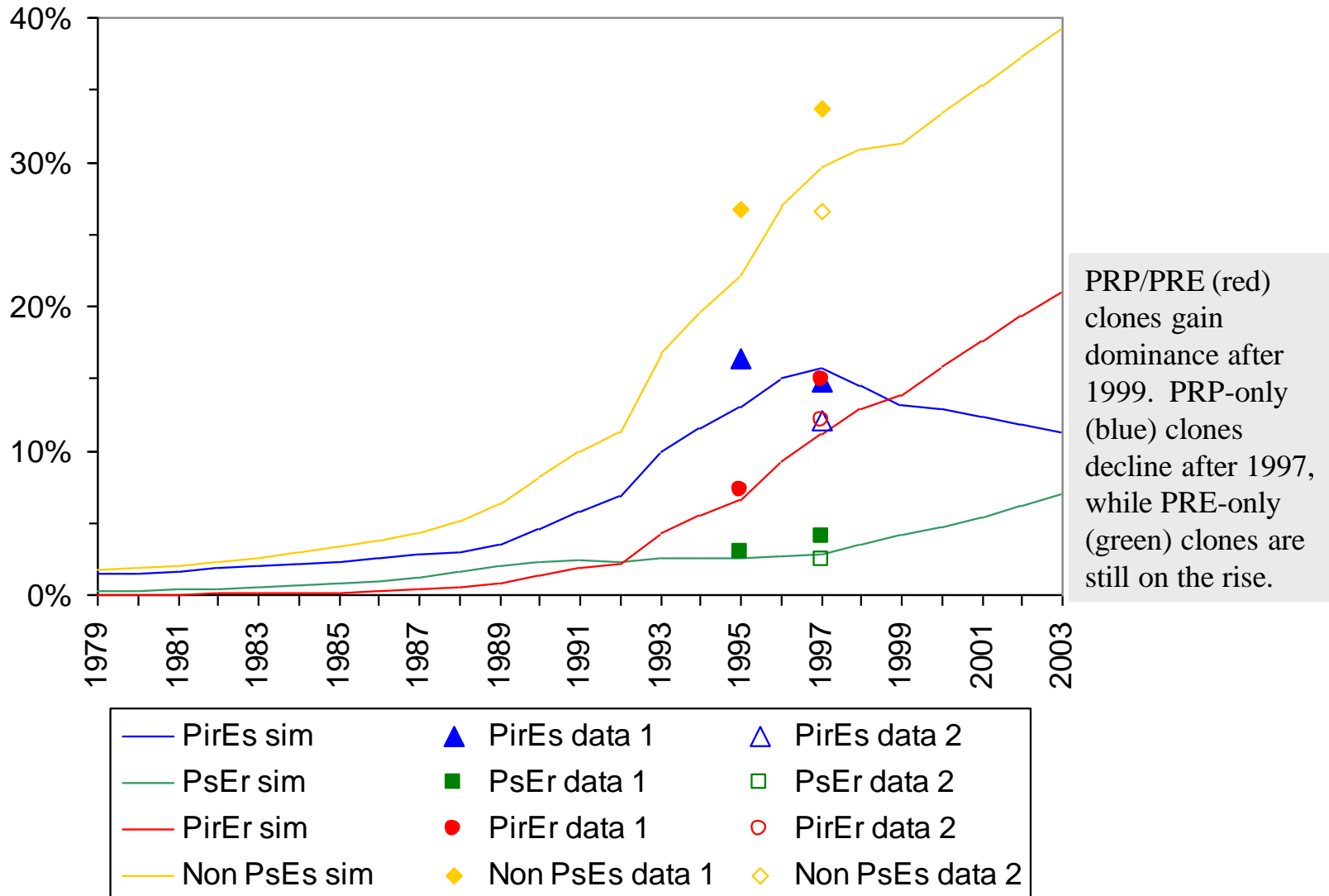
	USA		Spain		
	One-class	*Two-class*	*One-class*	*Two-class*	*Two-class calculation*
Ps	98.5%	98.5%	94.0%	94.6%	Ps = PsEs + PsEr
Pi	1.5%	1.4%	5.75%	5.0%	Pi = PiEs + PiEr
Pr	0%	0.02%	0.25%	0.5%	Pr = PrEs + PrEr
Es	99.7%	99.7%	99.0%	99.6%	Es = PsEs + PiEs + PrEs
Er	0.3%	0.3%	1.0%	0.4%	Er = PsEr + PiEr + PrEr

Clone types (two-class model)

PsEs	98.3%	94.3%
PsEr	0.23%	0.29%
PiEs	1.4%	4.9%
PiEr	0.03%	0.09%
PrEs	0.02%	0.44%
PrEr	0.001%	0.04%
total	*100.0%*	*100.0%*

Prevalence of pneumococcal clones with PRP (Pir: Pi or Pr) and/or PRE (Er) in the USA

PRP/PRE (red) clones gain dominance after 1999. PRP-only (blue) clones decline after 1997, while PRE-only (green) clones are still on the rise.

Sources: (1) Doern 1996, 1999, (2) Whitney 2000.

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Prevalence of pneumococcal clones with PRP (Pir: Pi or Pr) and/or PRE (Er) in Spain

PRP/PRE (red) clones gain dominance after 1997. PRP-only (blue) clones decline after 1990, while PRE-only (green) clones are still on the rise.

Multidrug Antibiotic Resistance - J. Homer et al.
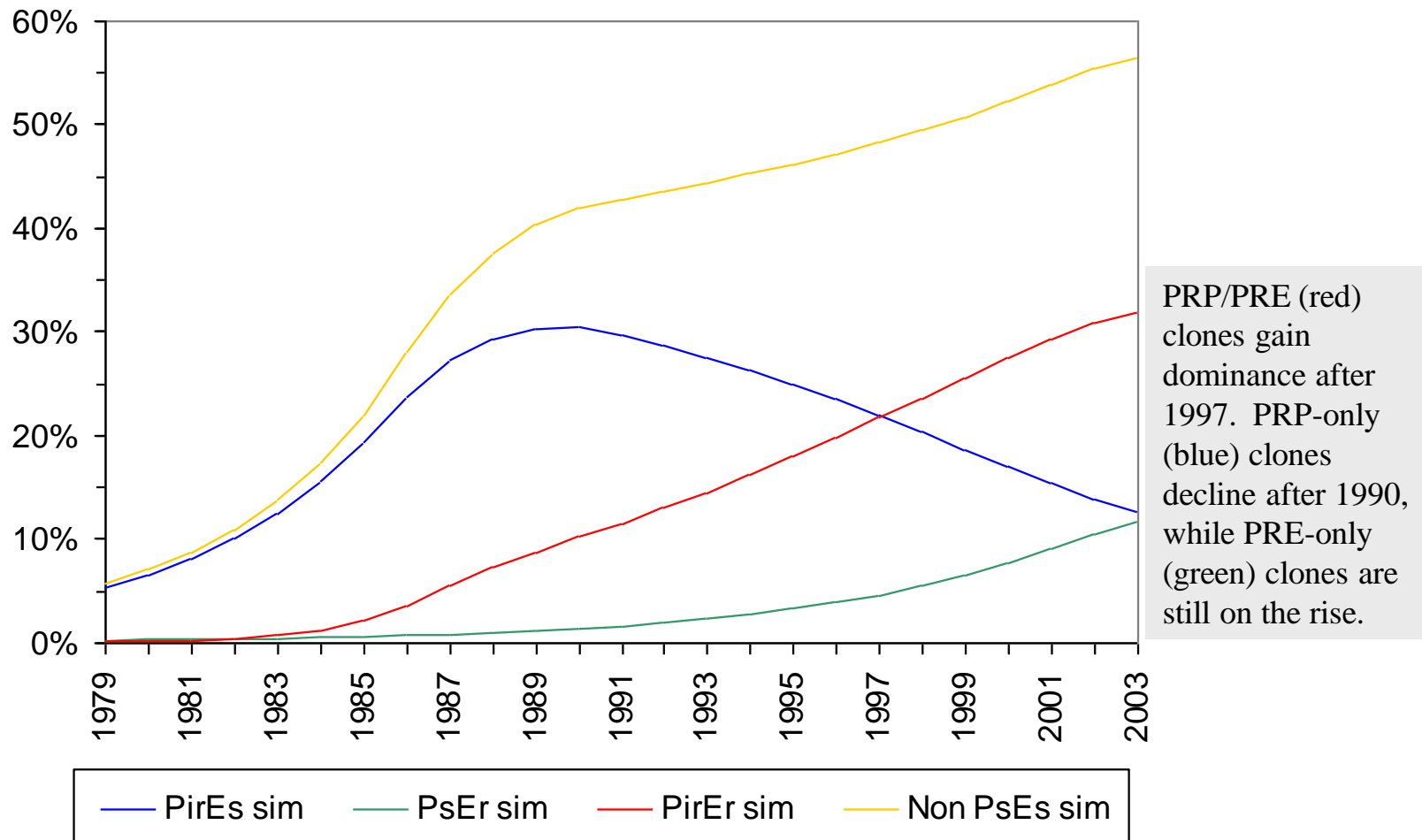
Prevalence of PRP (Pir) in clones with PRE (Er) in the USA and Spain
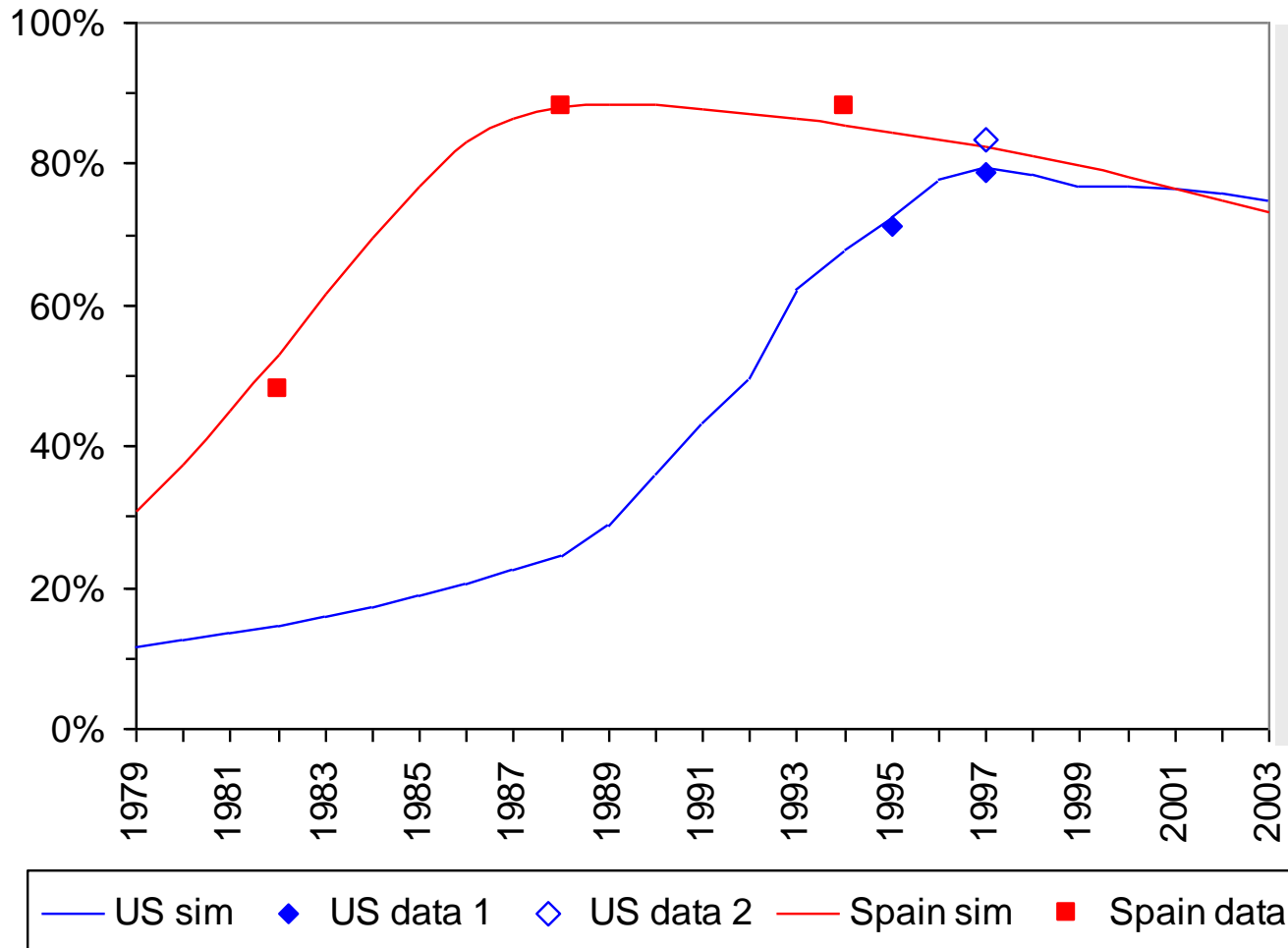
The great majority of clones with PRE also have PRP.
Until the late 1990s in the USA and the late 1980s in Spain, PRP/PRE clones had a significant reproductive advantage over those with PRE alone. With the decline in beta-lactam use in both countries, the fastest-growing clone type is now PRE-only, followed by PRP/PRE.

Sources: <u>USA</u>: (1) Doern 1996, 1999, (2) Whitney 2000; <u>Spain</u>: Fenoll 1998.

# Testing impacts of antibiotic use reduction

- Questions

  - How much reduction in use does it take to reverse the growth of two-drug resistance (PRP/PRE)?

  - Does it require large reductions in both drug classes sufficient to drive out *all* resistance, or is there an easier way?

- Procedure

  - In USA-calibrated model, assume constant use levels from 2002 onward; test various use reduction combinations

    - Base run: Continue use forward at assumed 1999-2001 levels

      - Beta-lactams = 190 Rxs/1000/year

      - Macrolides = 68 Rxs/1000/year

    - Test use above and below thresholds for resistance elimination

      - Beta-lactams for PRP elimination $\cong 140$ [historical low: 160.1 (1998)]

      - Macrolides for PRE elimination $\cong 50$ [historical low: 50.2 (1991)]

Reducing use of one class only:
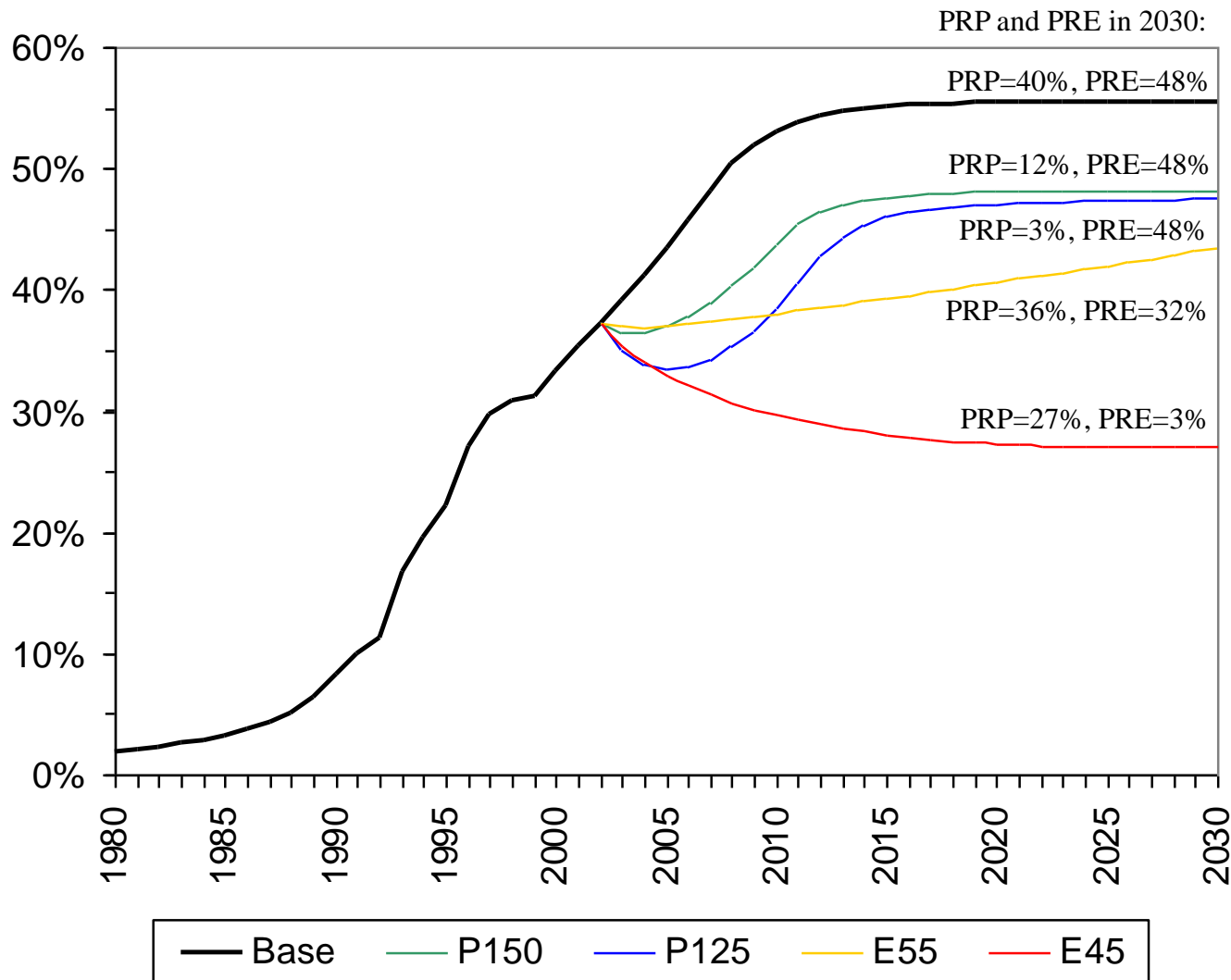# Prevalence of two-class resistant (PRP/PRE) clones
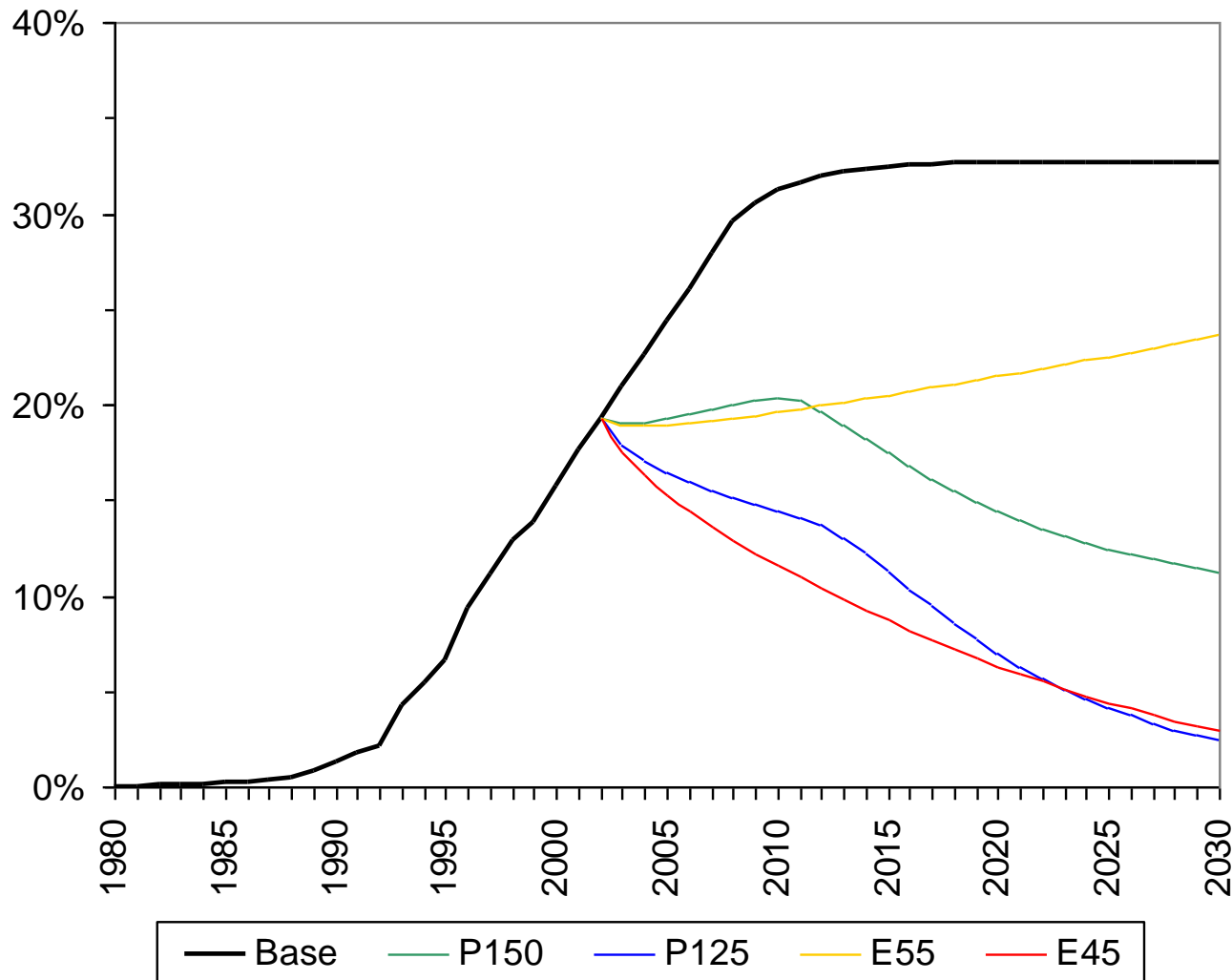
If use of either drug class is reduced below its elimination threshold (as in P125 and E45), two-class resistance is ultimately eliminated. Otherwise, reduction in use of one class only may allow two-class resistance to grow further (E55) or to decline but only partially and with a delay (P150).

Reducing use of both classes:
Prevalence of two-class resistant (PRP/PRE) clones
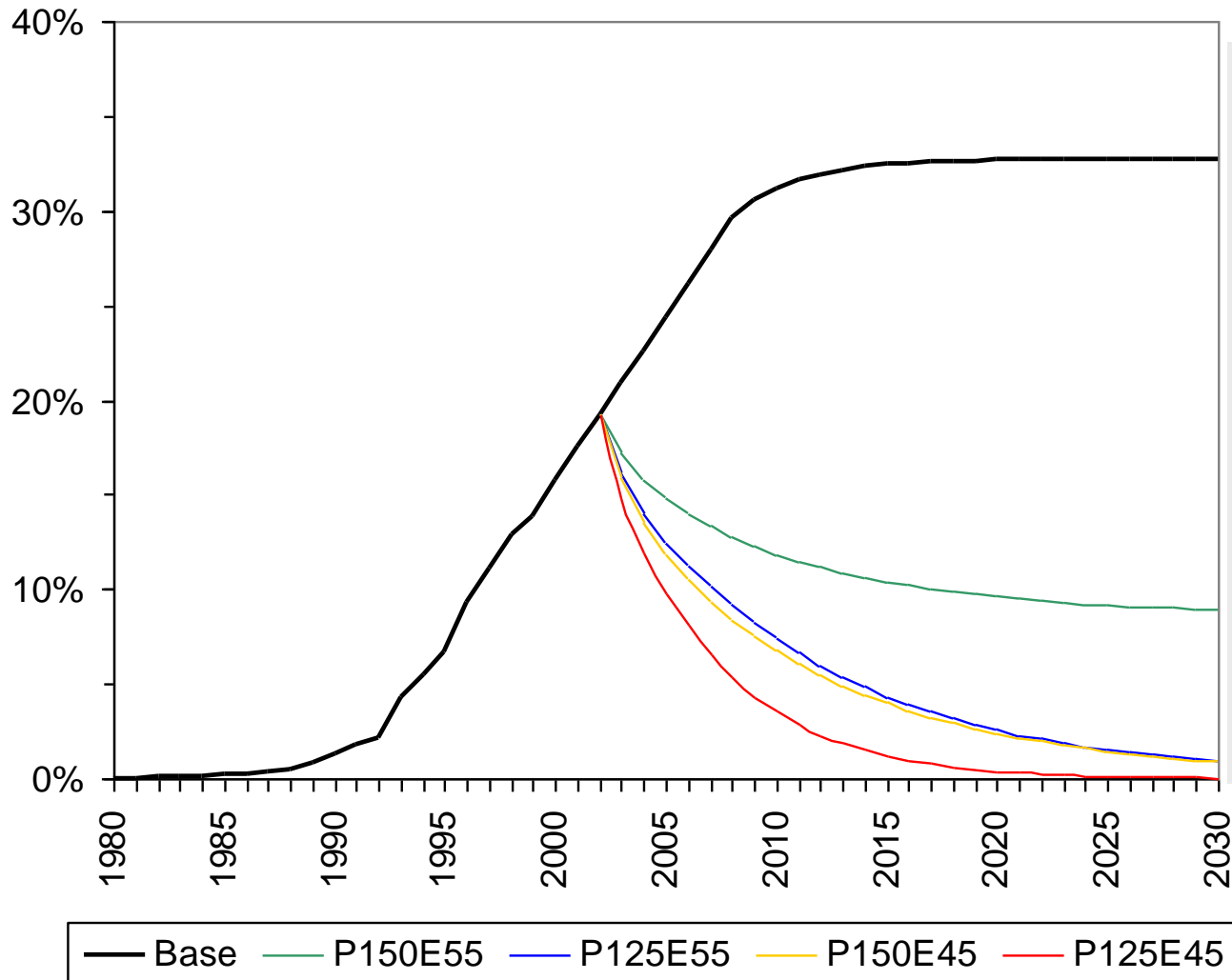
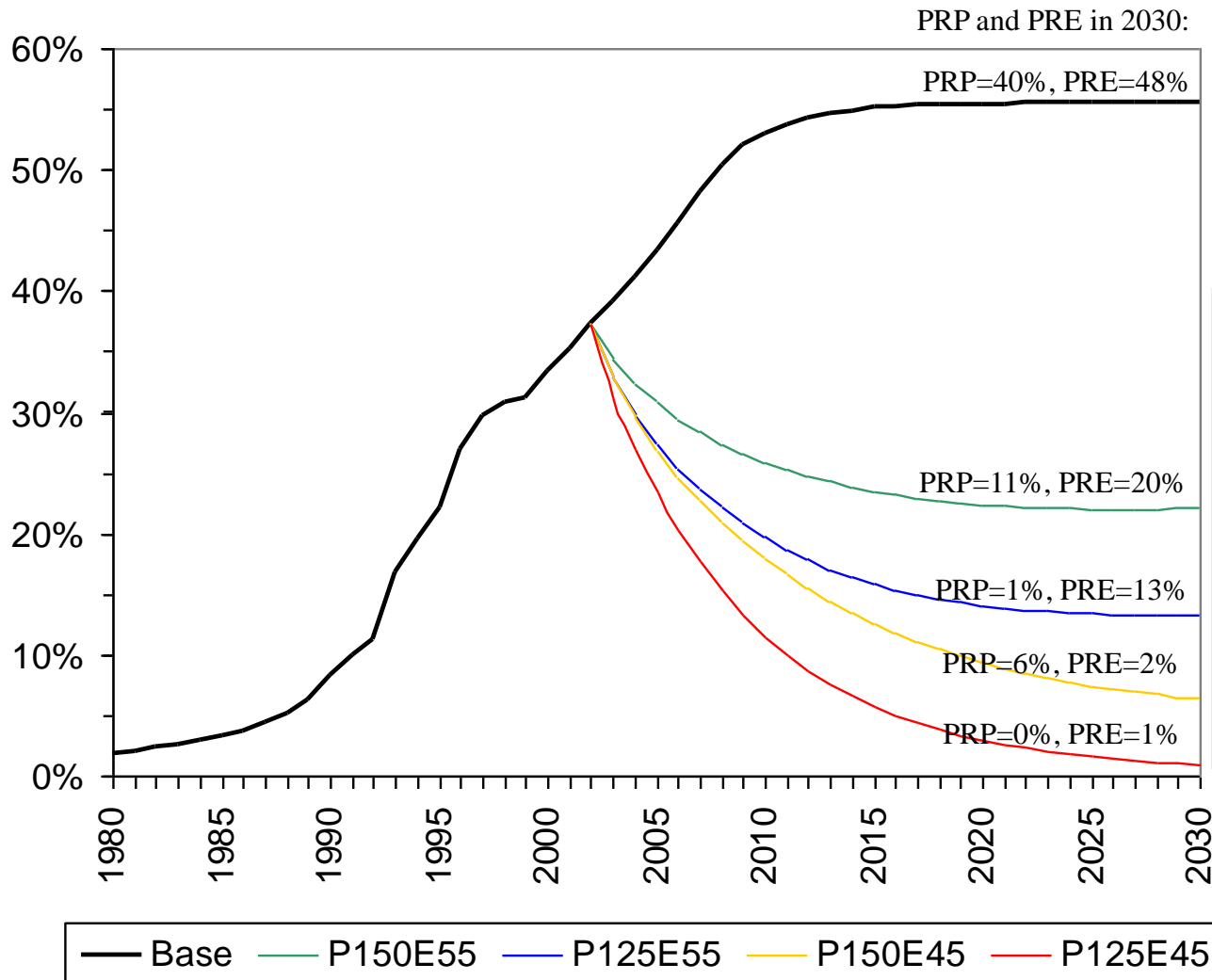Two-class resistance may be more effectively reversed when use of both drug classes is reduced. Quick reversal may be achieved even when use of both classes remains somewhat above their respective elimination thresholds (as in P150E55). However, ultimate *elimination* of two-class resistance still requires that use of at least one drug class be reduced below its threshold.

Legend: Base, P150E55, P125E55, P150E45, P125E45

Reducing use of one class only: Prevalence of one-class and two-class resistant (PRP and/or PRE) clones

PRP and PRE in 2030:

PRP=40%, PRE=48%

PRP=12%, PRE=48%

PRP=3%, PRE=48%

PRP=36%, PRE=32%

PRP=27%, PRE=3%

Legend: Base, P150, P125, E55, E45

If use is reduced for one drug class only, resistance to the other class will persist. The reduction in use may, however, take away the reproductive advantage of two-class resistant clones. If use of the one class is reduced below the elimination threshold (as in P125 and E45), resistance to the other class will ultimately be all one-class resistance.

Reducing use of both classes: Prevalence of one-class and two-class resistant (PRP and/or PRE) clones

PRP and PRE in 2030:

PRP=40%, PRE=48%

PRP=11%, PRE=20%

PRP=1%, PRE=13%

PRP=6%, PRE=2%

PRP=0%, PRE=1%

When use of both drug classes is reduced, the growth of both one-class and two-class resistance may be quickly reversed. This holds true even when use of both classes remains somewhat above their respective elimination thresholds (as in P150E55).

Base —— P150E55 —— P125E55 —— P150E45 —— P125E45

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Conclusions and Next Steps

- ## Conclusions

  - ### The two-class model is able to reproduce historical growth patterns of one-class and two-class pneumococcal resistance

    - The two-class model is a straightforward extension of the one-class model, with emphasis on *reproductive advantage* rather than mutation, including *co-transfer* of resistance genes

  - ### Reversal and ultimate elimination of two-class resistance can be achieved by reducing use of either of the two drug classes below its respective elimination threshold

    - But reducing use of the other drug class as well, even if not below the elimination threshold, can significantly speed that process

- ## Possible next steps

  - ### Seek more recent US data on resistance by clone type

  - ### Publish results in medical journal

  - ### Apply model to growing fluoroquinolone class

  - ### Apply model to a different pathogen

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