Antibiotic resistance: the bigger picture, a holistic viewpoint of outcomes and costs.

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The end of medicine as we know it Jim* !

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> **A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill.**

Dr Margaret Chan,
Director-General, World Health Organization. March 2012[2]

* For you Trekkies …Attributed to Gene Roddenberry 1975 app.

Antimicrobial resistance……

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- Antibiotic resistance is a global issue and is increasing
- Multi-drug resistant bacteria cause life threatening infections
- Antibiotics **cure** life-threatening infections.
- Other treatments that are used to treat life threatening conditions can cost upwards of $30,000 for a months course (e.g. the anticancer treatments Avastin, Folotyn).
- A course of Sovaldi to **cure** Hepatitis C costs **$84,000** which is frequently justified by the need to maintain innovation in R&D.
- Impact of antibiotics is clear and undisputed yet……

- Holistic means “upholds that all aspects of people's needs including psychological, physical and social should be taken into account and seen as a whole”.

Free life saving drugs- in the fresh commodity section

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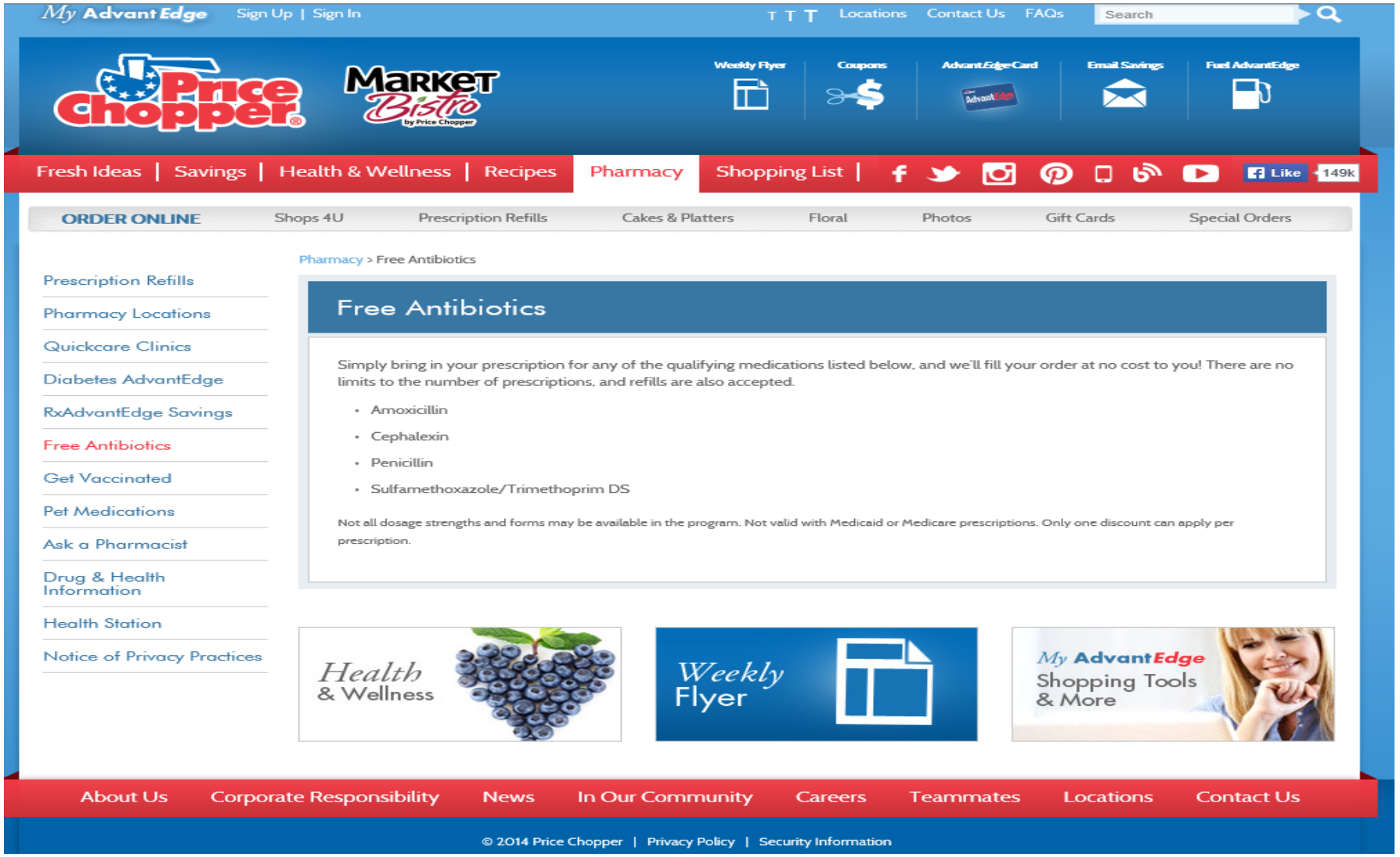

Recent US-based analysis: Societal values = holistic overview.

Eastern Research Group (ERG) tasked by US government to account for ALL costs involved in certain infections *

- **Comprehensive model for drugs for 6 key indications (ABOM, ABSSSI, CAP, cIAI, cUTI, HAP-VAP)[1]**
- **Current NPV of the new antibiotic is always < $40 million**
  - All 90% confidence intervals on estimate went below zero
- **Value to the patient was MUCH higher**
  - **Just based on the value of days of work and life restored, the value to society ranged from $500m to $12 billion**
- **Thus, this new holistic evaluation shows**
  - Starting antibacterial R&D is not financially rational, at least not with traditional R&D costs and approaches because……
  - **We (Society) undervalue these drugs**

* Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Eastern Research Group. Analytical framework for examining the value of antibacterial products. Report to US DHHS. http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

Table 1. Influences on studies assessing the impact of infection with antimicrobial-resistant bacteria.

Methodologic issue, factor	Aspects
Outcome	
Mortality	In hospital, attributable to infection; in hospital and after discharge, all-cause
Morbidity	Length of hospitalization, need for ICU care, need for surgery or other procedures, activity level at discharge, and loss of functional status (loss of work)
Economic	Hospital costs, hospital charges, resource utilization, total health care costs, skilled nursing, and other outpatient costs
Outcome perspective	
Hospital	Inpatient morbidity, mortality, and/or costs
Third-party payer	Inpatient and outpatient health care costs
Patient	Decreased functional status, loss of work, and fewer antimicrobial agent options
Societal	Total health care costs of antimicrobial resistance and loss of antimicrobial classes
Choice of reference group	
Patients infected with susceptible strains	…
Uninfected patients	…
Patients colonized with resistant strains	…
Confounding factors	
Length of hospital stay	APACHE score, McCabe/Jackson score, and Charlson comorbidity score[a]
Underlying severity of illness	…
Comorbid conditions	…

NOTE. ICU, intensive care unit. Adapted and reprinted with permission from Cosgrove and Carmeli [2].

[a] APACHE is a severity of disease classification system that uses a point score based on initial values of 12 routine physiologic measurements, age, and previous health status. It is a validated tool to predict mortality for patients in the ICU. The McCabe/Jackson score uses a simple 3-category score to predict mortality for patients with bacteremia due to gram-negative organisms. The Charlson comorbidity score is a simple, readily applicable, and valid method of estimating risk of death from comorbid disease.

Cosgrove S CID 2008

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ReACT information on the impact of antibiotic resistance

Bacteria	Death rate *resistant* strain	Death rate *sensitive* strain
E. coli[23]	32%	17%
A. baumannii[25]	16.4%	5.4%
A. baumannii[19]	53.8%	31.0%*
K. pneumoniae[26]	42.9% (CRKP)	18.9%
K. pneumoniae[27]	43.8% (CRKP)	12.5%
K. pneumoniae[10]	38%	12%
S. aureus[28]	36.4% (MRSA)	27.0%
S. aureus[14]	23.6% (MRSA)	11.5%

Table 2: Comparison of death rates (mortality) in patients with resistant or sensitive strains of bacteria. *=not fully sensitive.

ERG base data for “proper” evaluation of antibiotic value

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Table 15: Social EPV Model Parameters and Assumptions (Point Estimates)

Model Parameter/Assumption	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Real Annual Social Rate of Discount	3%					
% of Patients Not Responding to Existing Drugs	20%					
% Increase in Duration in Patients Not Responding to Existing Drugs	50%					
Loss in Quality of Life, Acute	0.11	0.36	0.15	0.5	0.27	0.17
Duration (days)	10	6	4	10	4	8.5
Loss in Quality of Life, Convalescence	0.04	0.36	0.1	0.15	N/A	N/A
Duration (days)	20	18	5	12	N/A	N/A
Lost QALYs per illness	0.0049	0.0239	0.0038	0.0023	0.0030	0.0040
Total Number of Cases per Year (unadjusted for population growth)	13,200,000	726,000	1,170,000	72,000	1,083,000	272,600
Mortality Parameters						
Deaths	0	1,923	51,683	14,554	36,900	81,779
Lost QALYs for Patients that Die	0	26,167	572,741	243,987	319,913	1,848,212
VSL per Patient	N/A	$5,623,708	$5,301,924	$5,585,504	$4,953,688	$4,770,000
Morbidity Parameters						
Number of Patients that Survive	13,200,000	724,397	1,118,000	57,489	1,045,986	190,818
Lost QALYs for Patients that Survive	65,248	17,336	4,295	1,632	2,432	756
WTP (VSLY*Lost QALYs) per patient	$1,124	$8,749	$1,113	$12,717	$758	$1,149

N/A = Not applicable
QALY = Quality-adjusted-life-year
VSL = Value of a statistical life
VSLY = Value of a statistical life year
WTP = Willingness-to-pay
The figures in the table are rounded for presentation purposes.

* Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Eastern Research Group. Analytical framework for examining the value of antibacterial products. Report to US DHHS. http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

Table 16: Reported Estimates of Antimicrobial Resistance

Source	% of Patients Resistant to Commonly Used Antibacterial Drugs
Evans, et al., 2007 [a]	23.0%
Roberts, et al., 2009 [b]	13.5%
ECDC/EMEA Joint Technical Report, 2009 [c]	
Methicillin-resistant *S. aureus* (MRSA)	25.0%
Vancomycin-resistant *Enterococcus faecium*	8.0%
Penicillin-resistant *S. pneumonia*	4.0%
Third-generation cephalosporin-resistant *E. coli*	9.0%
Third-generation cephalosporin-resistant *K. pneumoniae*	20.0%
Carbapenem-resistant *P. aeruginosa*	19.0%
Expert 1	
Inpatient	30.0%
Outpatient	10.0% - 15.0%
Expert 2	20.0% - 25.0%

[a] Based on a sample of 604 surgical admissions treated for at least one Gram-negative rod (GNR) infection [b] Based on a sample of 1,391 patients in a Chicago area hospital

[c] Based on European Antimicrobial Resistance Surveillance System (EARSS) for EU Member States, Iceland and Norway for each year during the period 2002–2007

- Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Eastern Research Group. Analytical framework for examining
- the value of antibacterial products. Report to US DHHS. http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

MRSA- costs and facts

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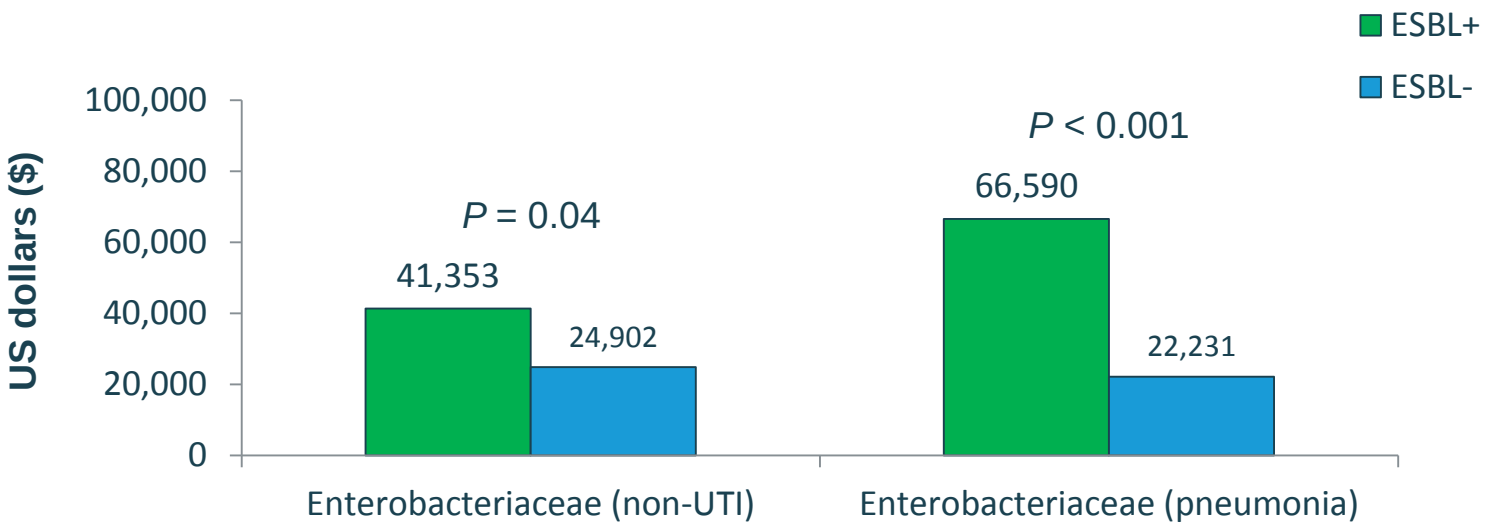
- **In USA costs >$560 million to third party payers.**
- **Lost productivity amounts to $>2.7 BILLION.**
- **Direct costs for CA MRSA are around 25% of total costs.**

Disease	Est costs per case ($)
CA MRSA	7,070-20,489
Influenza	3,000-4,000
Foodborne illness	1,851
Pertussis	1,952
Lyme disease	397-923

Lee BY, Singh A, David M et al Clin Micro Inf 2013,19: 528-536.

ESBL Infections Are Associated With Higher Mean Hospital Costs (US)

- **Systematic literature review of 8 studies on the costs of ESBL-producing Enterobacteriaceae**



P value for difference in cost between ESBL+ vs ESBL- infections.

ESBL, extended-spectrum β-lactamase; MDR, multidrug resistance; UTI, urinary tract infections.
Tansarli et al. *Expert Rev Anti Infect Ther.* 2013;11:321-31.

Multidrug-resistant (MDR) *Pseudomonas aeruginosa* Is Associated With Increased Morbidity and Mortality

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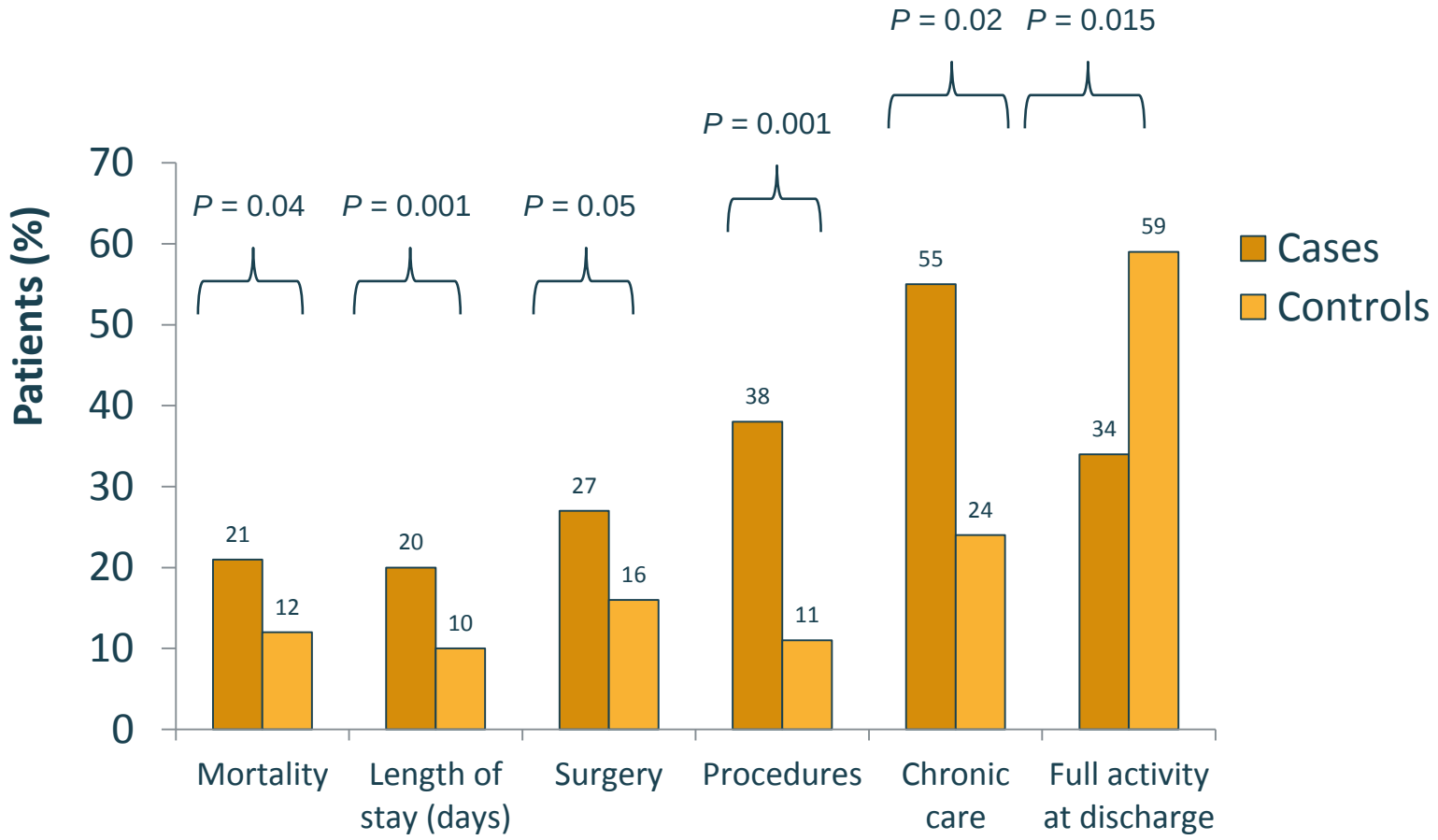
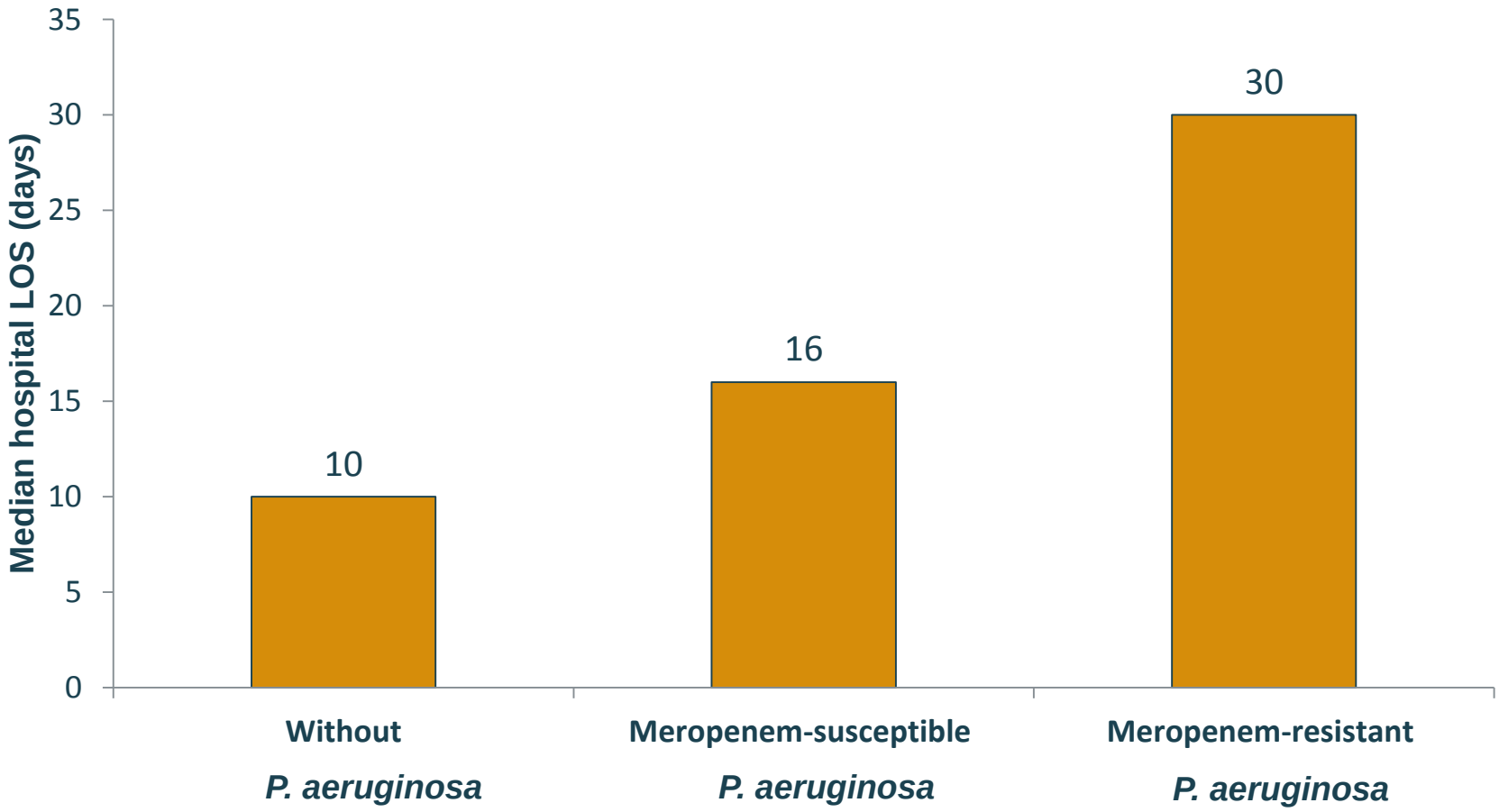
Retrospective study at Tel-Aviv Sourasky Medical Center, Israel; 82 patients with MDR P. aeruginosa and 82 controls. More severe outcomes with MDR *P. aeruginosa*.



Aloush et al. *Antimicrob Agents Chemother*. 2006;50:43-6.

Length of Stay* Increases With Drug Resistance



P **< 0.001 for meropenem resistant *P. aeruginosa* vs other comparators.**
LOS, length of stay.
Eagye et al. *Infect Control Hosp Epidemiol.* 2009;30:746-52. *** also drives increased costs to relatives.**

Impact of resistance on *Acinetobacter baumannii* (ACB) infections.

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- Timeline: 2009-Q3/2013.
- Locations: 152 US hospitals
- Confirmed ACB infections.
- 376 MDR ACB in primary pneumonia
- 1,869 MDR ACB in primary sepsis.

Parameter	Pneumonia		Sepsis	
	MDR ACB	Non MDR ACB	MDR ACB	Non MDR ACB
Length of hospital stay (days)	13.4	10.5	16.2	14.8
ICU stay required %	46.6	22.6	62.8	46.8
Mortality %	15.3	5.9	21.7	16.9
Hospital costs $	32,086	24,367	43,997	38,494

LaPensee K et al IDWeek 2014 Abstract 338

Clinical Outcomes of *P.aeruginosa* Pneumonia in ICU Patients

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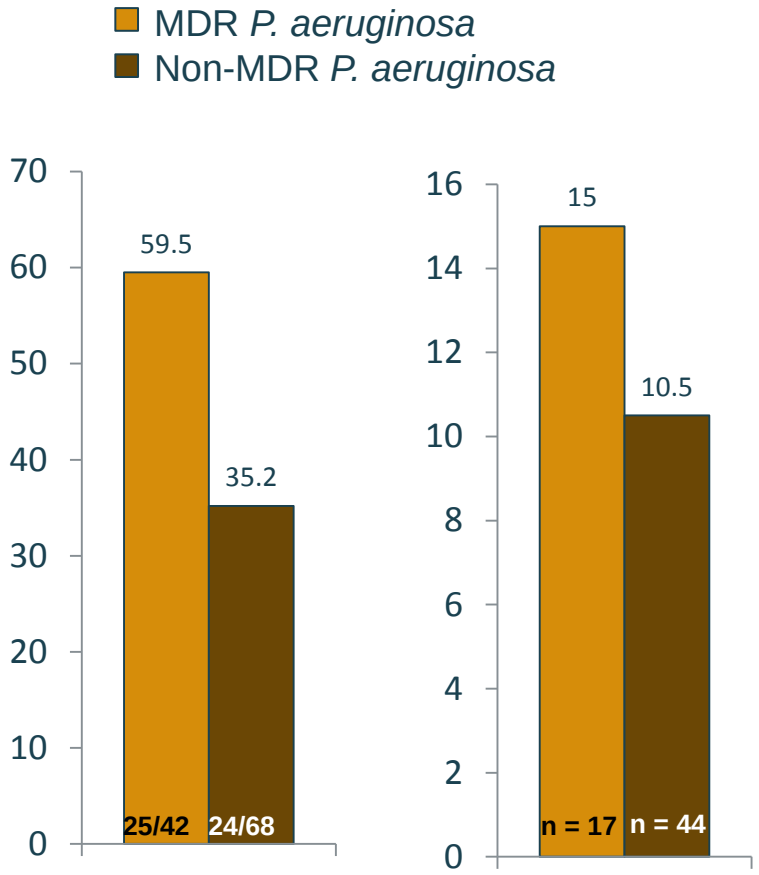
- **Retrospective analysis of 110 ICU patients with culture-confirmed *P. aeruginosa* pneumonia in Italy**
  - Approx. 80% isolates were drug resistant
    - 38% multidrug resistant (MDR)
  - Overall ICU mortality = 44.5%
  - MDR *P. aeruginosa* ICU mortality = 59.5%
- **In logistic regression, inadequate initial antibiotic therapy (IIAT), diabetes mellitus, elevated Simplified Acute Physiology Score II, and older age were independently associated with ICU mortality**
- **MDR in the *P. aeruginosa* isolate can significantly increase the need for mechanical ventilation**



Tumbarello et al. *Intensive Care Med.* 2013;39:682-92.

The value of new antibiotics is clear.

- **Obvious clinical need**
- **Global healthcare mandate for new drugs is vital**
- **Net Present Value is unambiguous**
- **MDR infections are clearly “bad news”**
  - More deaths, so the value of a life is obvious
  - Longer hospital or Unit stay
  - Lost productivity of patient and many family members
  - Efficacy of new antibiotics is undisputed
  - Impact of inappropriate or/and generic drugs is clear and not debated.

Value of a Statistical Life (VSL)

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- To calculate VSL, we first took the value of a statistical life reported in 2000 dollars by age group from Aldy & Viscusi (2008).
- Next, it was necessary to adjust the VSL values by age group to capture changes in real income as well as prices from 2000 to 2011.
- Current data from the U.S. Bureau of Economic Analysis (BEA) show that the real personal income per capita was $28,888 in the year 2000 and $32,635 in 2012 (both in 2005 dollars), yielding a growth rate of 13 percent over this span of time.
- Hammitt & Robinson (2011) report that U.S. regulatory agencies generally assume that a 1.0 percent change in real income over time will result in a 40 to 60 percent change in the VSL.
- Using the midpoint of this range (50 percent), we inflated the reported VSL values by age group by 1.065 (= 1 + [0.5 × 0.13]) to account for changes in real income from 2000 to 2011.
- To adjust the VSL values for price changes, we used the general consumer price index-based inflation calculator (available on the Bureau of Labor Statistics website) that shows an average price increase of approximately 31 percent over the same time period.
- We then calculated the age-specific VSLY and apply it to

  the estimated number of years of life lost for each condition

Easy huh?

Antibacterials: the big mismatch 2014 !!

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Industry returns for a new antibiotic per indication (Figures in $ Millions)

Indication	Private Value (in $ Million)		
	90% Lower Bound	Mean	90% Upper Bound
ABOM	-$18.8	-$2.7	$215.1
ABSSSI	-$15.8	$27.1	$198.9
CABP	-$17.6	$37.4	$330.0
CIAI	-$18.0	$8.9	$222.5
CUTI	-$16.3	$21.9	$213.0
HABP/VABP	**-$23.5**	**-$4.5**	**$126.7**

-$4.5

Sertkaya A, Outterson K, et al. "Analytical Framework for Examining the Value of Antibacterial Products"
http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

Antibacterials: the HOLISTIC viewpoint 2015

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Social returns for a new antibiotic per indication (Figures in $ Millions)

Indication	Social Value		
	Min	Mean	Max
ABOM	$48	$486.6	$5,363
ABSSSI	$58	$584.2	$6,133
CABP	$706	$9,375.3	$72,494
CIAI	$114	$1,069.2	$10,231
CUTI	$674	$6,064.6	$54,795
HABP/VABP	**$1,068**	**$12,165.6**	**$161,335**

NEW NPV
$12,165.6

Sertkaya A, Outterson K, et al. "Analytical Framework for Examining the Value of Antibacterial Products"
http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm

The Bacterial Challenge in Europe: Time to React

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- Estimates in 2007 show that together, third-generation cephalosporin-resistant *Escherichia coli*, third-generation cephalosporin-resistant *Klebsiella pneumoniae*, and carbapenem-resistant *Pseudomonas aeruginosa,* were responsible for:
  - 193,300 cases of infection
  - 18,200 excess deaths
  - 1,375,0000 extra hospital days
    - With *P. aeruginosa* accounting for 141,900 infections, 10,200 deaths, and 809,000 extra hospital days
  - €503,100,000 extra in-hospital costs
  - €4,500,000 extra outpatient costs
  - €59,300,000 productivity losses due to absence from work
  - €300,300,000 productivity losses due to patients who died from their infection

"It is likely that the human and economic burden caused by antibiotic resistant Gram-negative bacteria…represents a major challenge to appropriate therapy, prevention and control in the foreseeable future."

ECDC/EMEA Joint Technical Report 2009: The bacterial challenge: time to react. http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

So to the bigger picture

- So how do antibiotics compare in “value” with other therapeutics?
- Bearing in mind the usual number of MDR infections which have a significant impact on management costs and Societal dues.

Comparison of Estimated number of Orphan Disease subjects/country

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Drugs	Disease area	Prevalence /100,000	Est # patients France	Germany	Italy	Spain	UK
Esbriet	IPF	17	11,220	13,770	10,200	7,820	10,880
Exjade	Fe overload	27	27,820	21,870	16,200	12,420	17,280
Gilenya	**MS**	**60-90**	**49,500 (mid)**	**60,750**	**45,000**	**34,500**	**48,000**
Kuvan	PKU	50	33,000	40,500	30,000	23,000	32,000
Signifor	Cushings	1-9	3,300 (mid)	4,050	3,000	2,300	3,200
Tracleer	PAH	1-9	3,300	4,050	3,000	2,300	3,200
	BSI*		**34,000**	**30,058**	**44,888**	**38,625**	**29,346**
	HAP*		67,139	99,192	61,366	40,673	54,951
	UTI*		99,574	180,348	44,888	38,625	29,346

*** These are total estimates for the 3 infections, the actual incidence of MDR infections is less but probably <15% overall. NB most are <200K in incidence**

Sources- MIMS, orphanet, PR Newswire & Datamonitor.

Comparison of Orphan Drug Annual Costs (ex=manufacturer)

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Drugs	Disease area	Prevalence /100,000	Year EMA approved	Unmet need	France Euros	Germany Euros	UK Pounds
Esbriet	IPF	17	2011	M	24,600	29,300	25,700
Exjade	Fe overload	27	2006	M/H	35,000	38,200	24,500
Gilenya	**MS**	**60-90**	**2011**	**M**	**22,700**	**17,000**	**19,200**
Kuvan	PKU	50	2008	H	76,500	69,000	70,900
Signifor	Cushings	1-9	2012	H	15,300	12,700	13,100
Tracleer	PAH	1-9	2022	M/H	25,800	32,400	19,700
Zavesca	Gauchers	1-9	2022	M/H	85,700	91,000	51,300

Orphan disease = A rare disease or disorder is defined in the U.S. as **one affecting fewer than 200,000 Americans**.

Sources- MIMS, orphanet, PR Newswire & Datamonitor.

Preserving antibiotics rationally……

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- **According to calculations a 1% reduction in the usefulness of existing antibiotics could impose costs of $600billion to $3trillion in lost human health!!**
- **WEF 2013- reported a negative impact of 0.4-1.6% on GDP by nation.**

On top of destabilizing our health systems, there are profound cost implications for economic systems and for the stability of social systems. The annual cost to the US health care system of antibiotic-resistant infections is already estimated at between US$ 21 billion to US$ 34 billion.[11] Elsewhere, losses to GDP have already been estimated at 0.4% to 1.6%.[12] The consequences of

Hollis A & Ahmed Z 2013 New Engl J Med, 369;2474-2477.

Justum pretium

- Justum pretium = just price or “fair value”
- By moral necessity “*price must reflect worth*”
- If a new antibiotic is more efficacious than current vs MDR pathogens then it should be priced to give “good or fair value”.
- The overall Societal costs of antibiotic resistance is massive and unrecognized.
- Not suggesting all new antibiotics be “orphan priced” but…….
- Current regulatory approaches could better reflect orphan methods to normalize the field.
- The “market” by MDR infection is too small to provide an adequate ROI….. Thus our valuation and perception must shift if we are to encourage pharma to continue to develop new antibiotics..

THERE IS ALWAYS SOMEONE...

... WHO WILL DO IT CHEAPER!