A Voice For Children: Promises and Potential

Gregory L. Kearns, PharmD, PhD, FAAP
Senior Vice President and Chief Research Officer,
Arkansas Children's, Inc.
President, Arkansas Children's Research Institute
Ross and Mary Whipple Family Distinguished Research Scientist
Professor of Pediatrics, University of Arkansas for Medical Sciences

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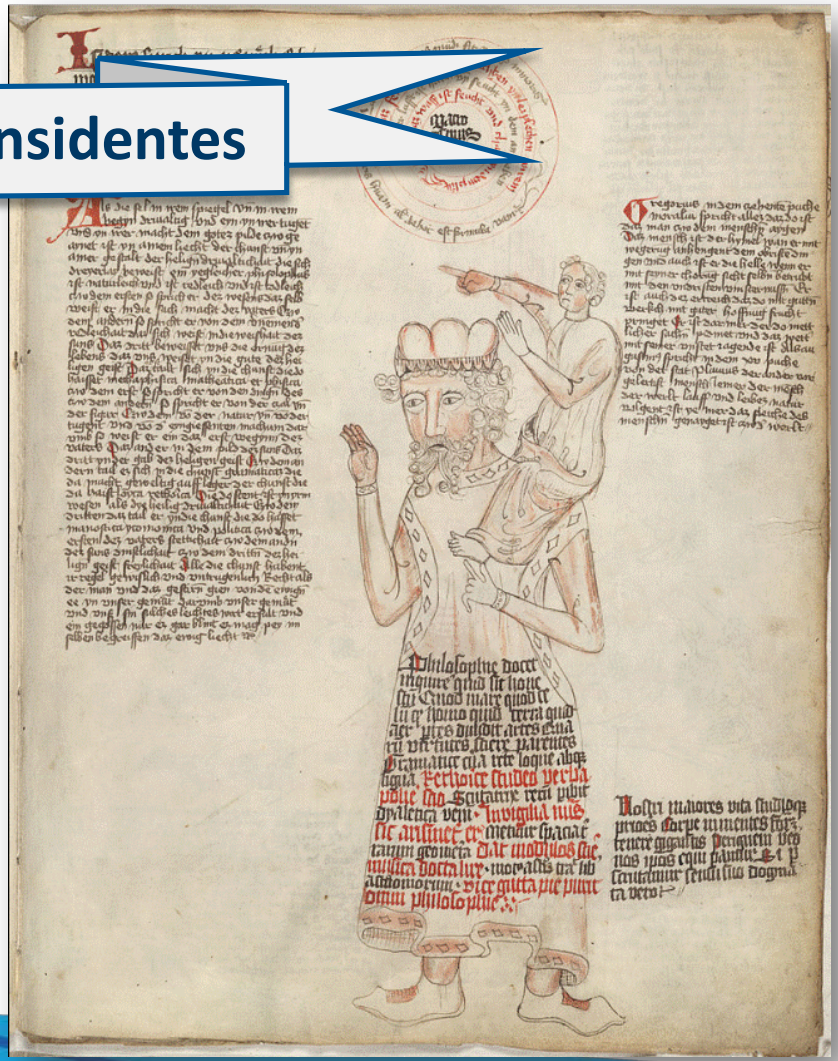
nanos gigantium humeris insidentes

"Bernard of Chartres used to say that **we are like dwarfs on the shoulders of giants**, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size."

- John of Salisbury, 1159



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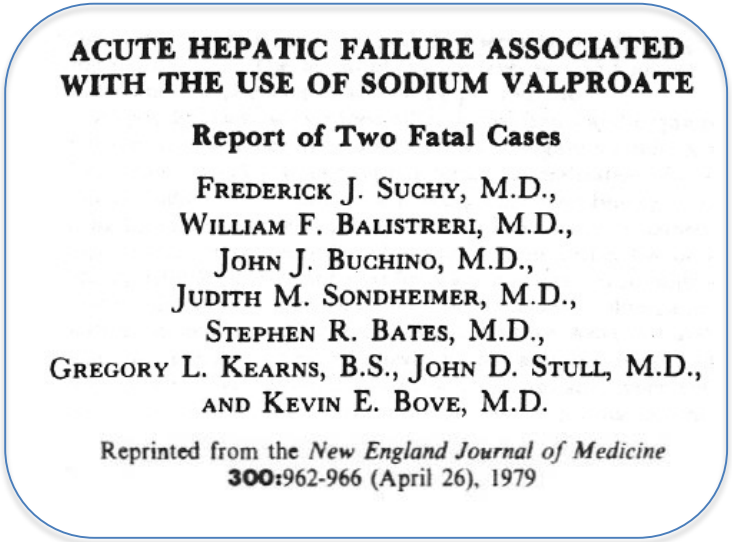

ACUTE HEPATIC FAILURE ASSOCIATED WITH THE USE OF SODIUM VALPROATE

Report of Two Fatal Cases

FREDERICK J. SUCHY, M.D.,
WILLIAM F. BALISTRERI, M.D.,
JOHN J. BUCHINO, M.D.,
JUDITH M. SONDHEIMER, M.D.,
STEPHEN R. BATES, M.D.,
GREGORY L. KEARNS, B.S., JOHN D. STULL, M.D.,
AND KEVIN E. BOVE, M.D.

Reprinted from the *New England Journal of Medicine*
300:962-966 (April 26), 1979

"…The data points (n = 10) were plotted as a semi-logarithmic relationship…. These data were based on the open, one-compartment model for extravascular administration….We obtained the elimination rate constant (Kel) of 0.02247hr $^{-1}$… We calculated the distribution coefficient and the total clearance on the basis of all previous doses using a modification of the superposition method.."

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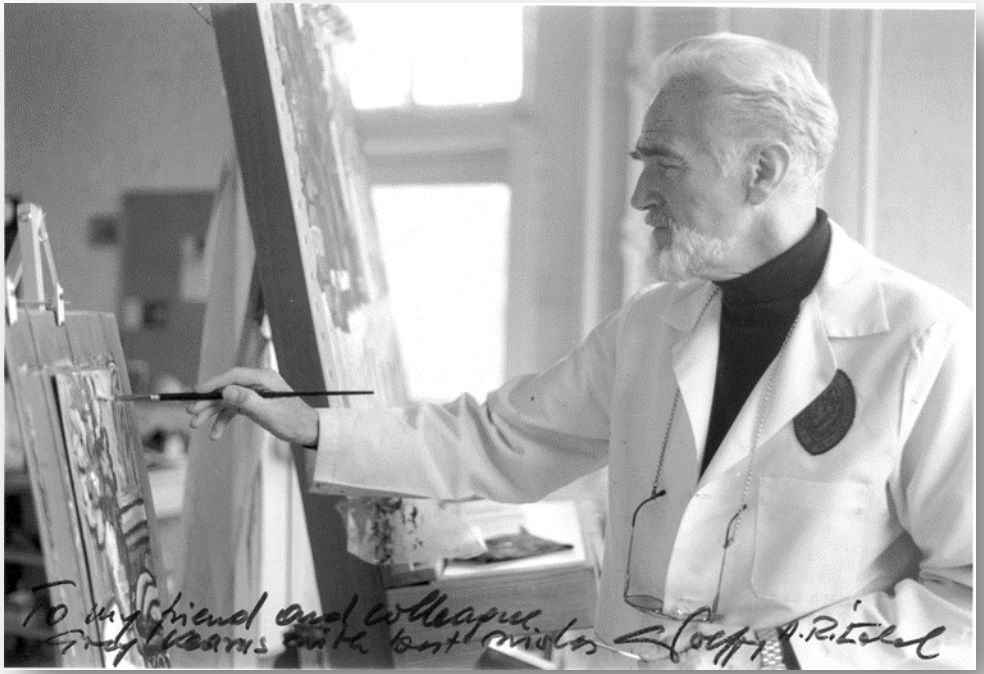

A teacher affects eternity; he can never tell where his influence stops.

From *The Education of Henry Adams*, ch. 20; 1907

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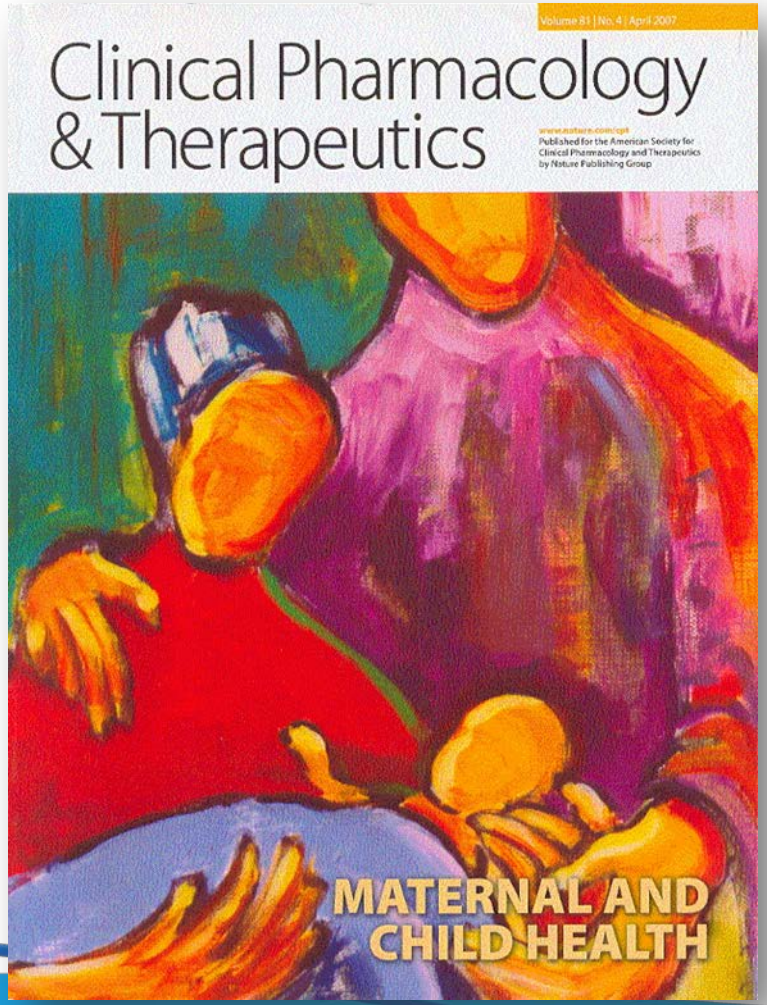

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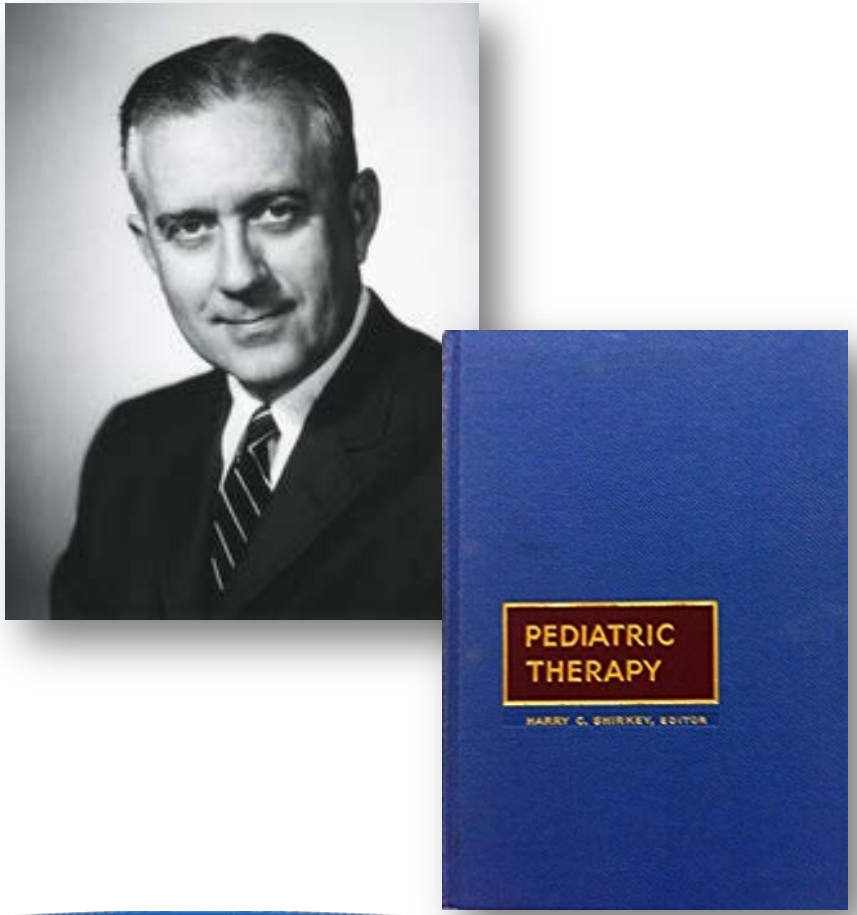

By an odd and unfortunate twist of fate, infants and children are becoming **“therapeutic or pharmaceutical orphans.”** Since 1962 they have been denied the use of many new drugs.

Pediatrics 1999;104:583

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TABLE 3. Current Status Regarding NMEs Approved*

	1995	1996
Number of NMEs approved	28	53
# Potential pediatric use (% NMEs)	20 (71)	32 (60)
# Pediatric studies or labeling	4	N/A
% Of NMEs	14	
% Of potential pediatric use	20	
% Difference for NMEs (studied–potential)	−57	

* Data from FDA with potential use ascertained by author. N/A indicates data not yet available.[12]

TABLE 4. Pediatric Off-label Prescribing*

Drug	Age Disclaimer	Off-label Frequency
Albuterol (inhalation solution for nebulization)	<12 y	1 626 000
Phenergan	<2 y	663 000
Ampicillin (IV or IM injection)	<12 y	600 000 (<16 y)
Zoloft	All ages	248 000 (<16 y)
Alupent (syrup)	<6 y	184 000
Beclomethasone diproprionate (nasal sprays)	<6 y	173 000
Lotrisone cream	<12 y	325 000
Prozac (pulvules and liquid)	<12 y	349 000
Intal		
Nebulization soln.	<2 y	109 000
Inhalation aerosol	<5 y	399 000
Ritalin (SR tablets)	<6 y	226 000

* Adapted from FDA Pediacom analysis of IMS survey of outpatient prescribing by 2940 physicians representing seven specialties (Pinas, 1996).[13]

Wilson J.T. (1999) *Pediatrics* 104(3);585-590.

COMMENTARIES

Pediatric Drug Development: Outlook for Science-Based Innovation

Dionna J. Green, IssamZineh and Gilbert J. Burckart

There has been significant progress in pediatric drug development during the past 15 years. Results from 1,200 pediatric studies have been submitted to the US Food and Drug Administration (FDA). Over 700 drug labels have been revised with information to guide pediatric use. Two international pediatric trial networks have been established. The failure rate for pediatric efficacy trials has fallen from over 40% to about 20%. Taken together, the outlook for pediatric drug development is positive.

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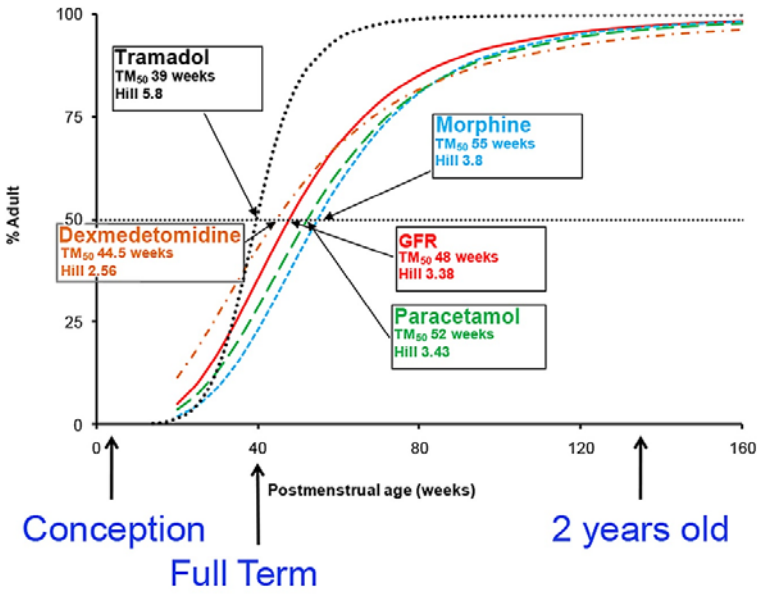
Maturation of Renal and Metabolic Function

Clearance Maturation



Maturation is predictable
– complete by 2 years of age –

– then Size is the main predictor of drug clearance

Holford and Anderson. Prediction of morphine dose in humans. *Paediatr Anaesth*. 2012 Mar;22(3):209-22.

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Challenges and Opportunities in the Development of Medical Therapies for Pediatric Populations and the Role of Extrapolation

Jeffrey S. Barrett, Raafat Bishai, Christina Bucci-Rechtweg, Amy Cheung, Solange Corriol-Rohou, Sebastian Haertter, Angela James, Steven J. Kovacs, Jing Liu, Dennis Potempa, Ashley Strougo, Konstantina Vanevski for the IQ consortium – CPLG Pediatric Working Group

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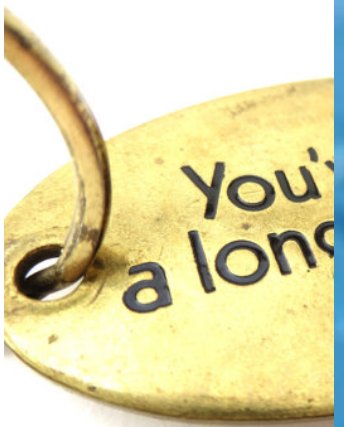

lever Is”

Debbie Field

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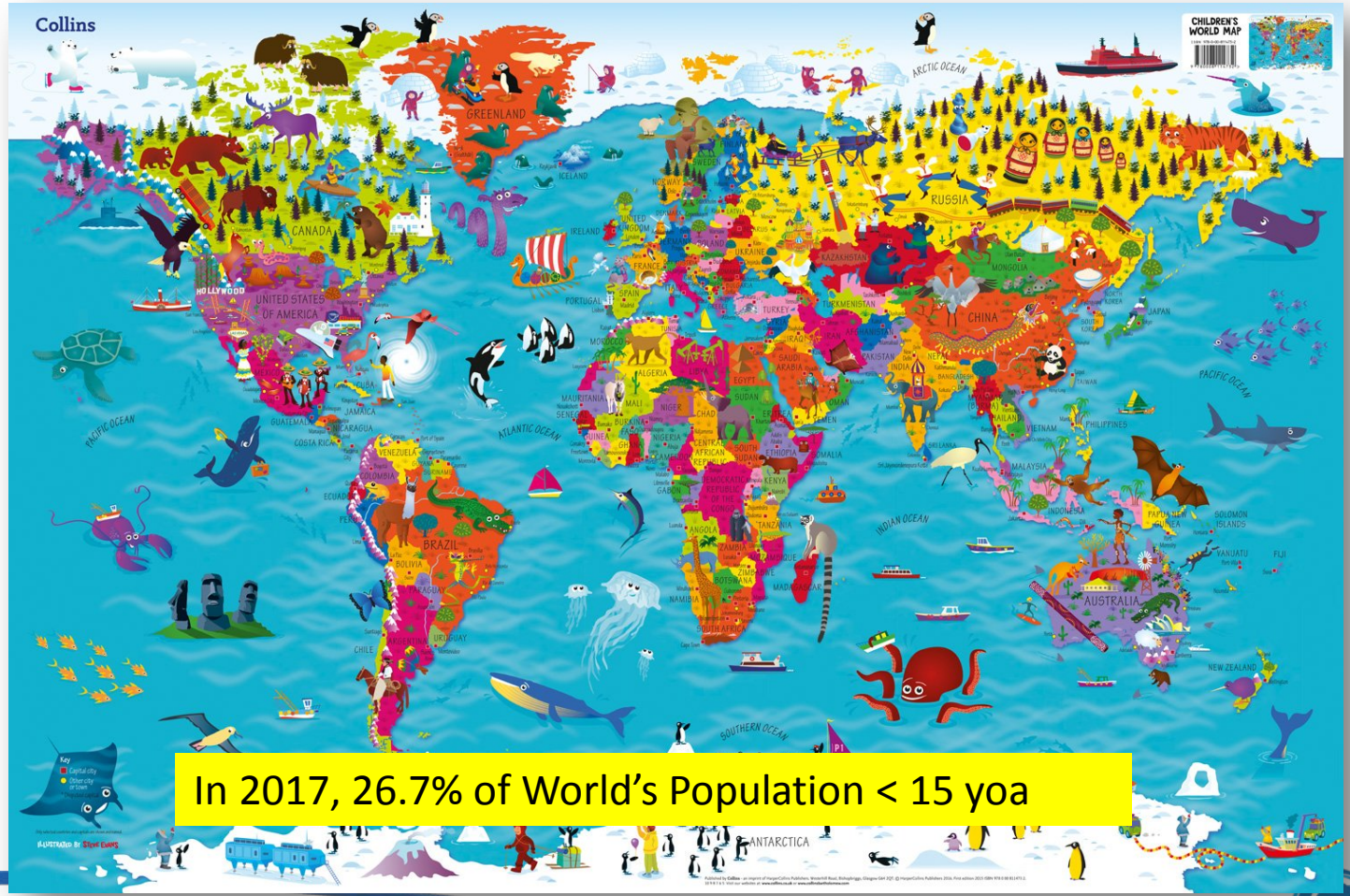

In 2017, 26.7% of World's Population < 15 yoa

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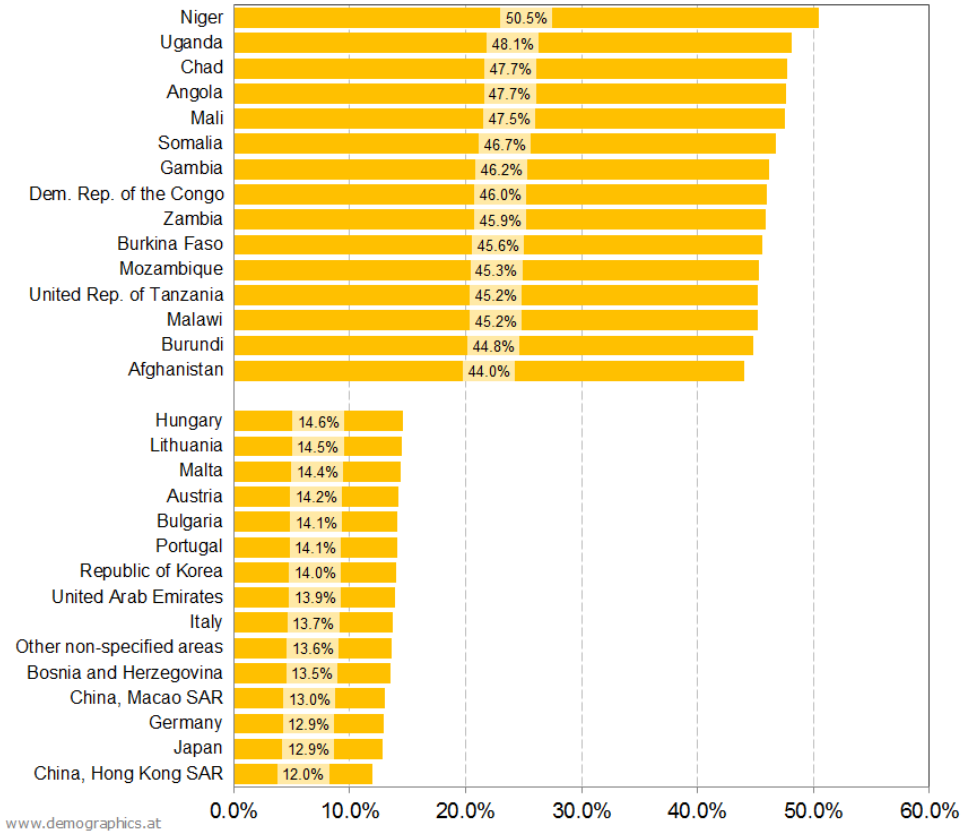
Percentage of Children in Various Countries



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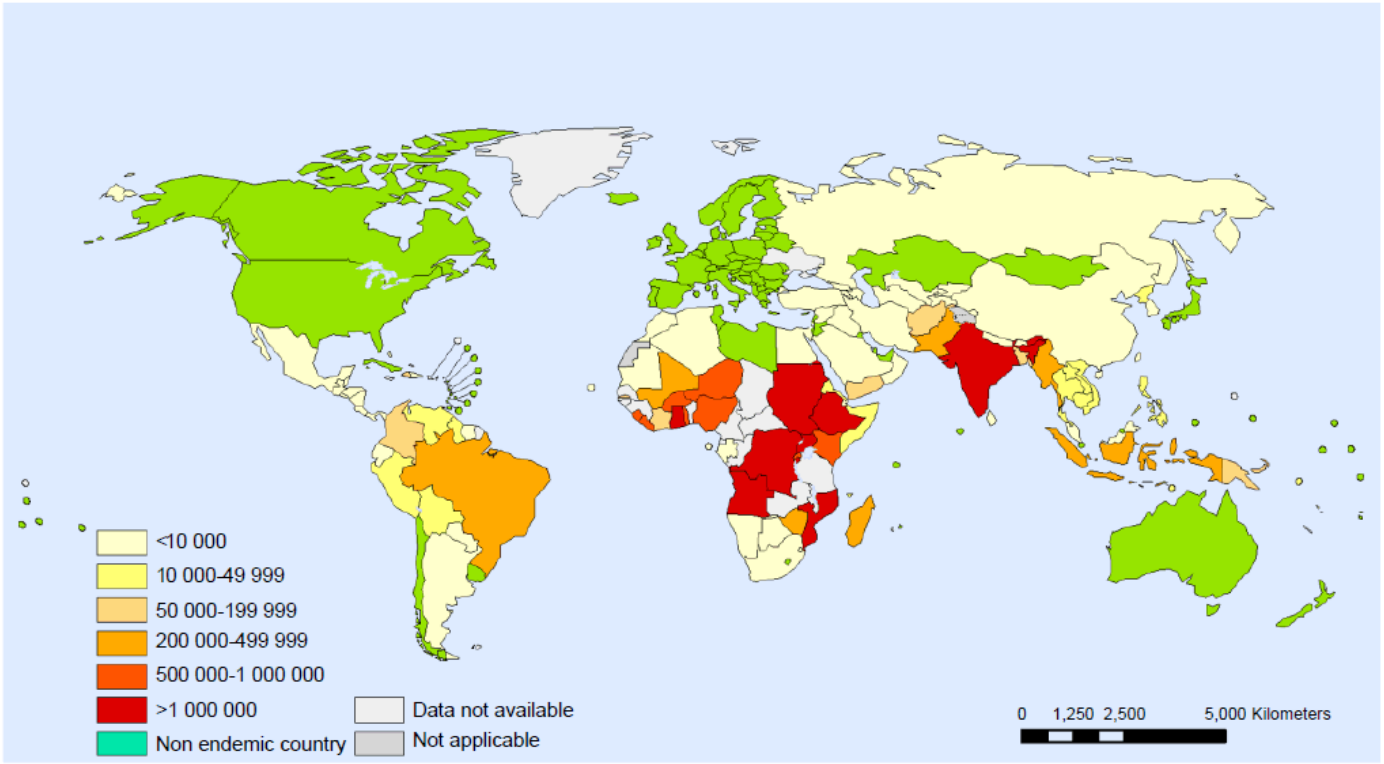
Number of malaria reported confirmed cases, 2010

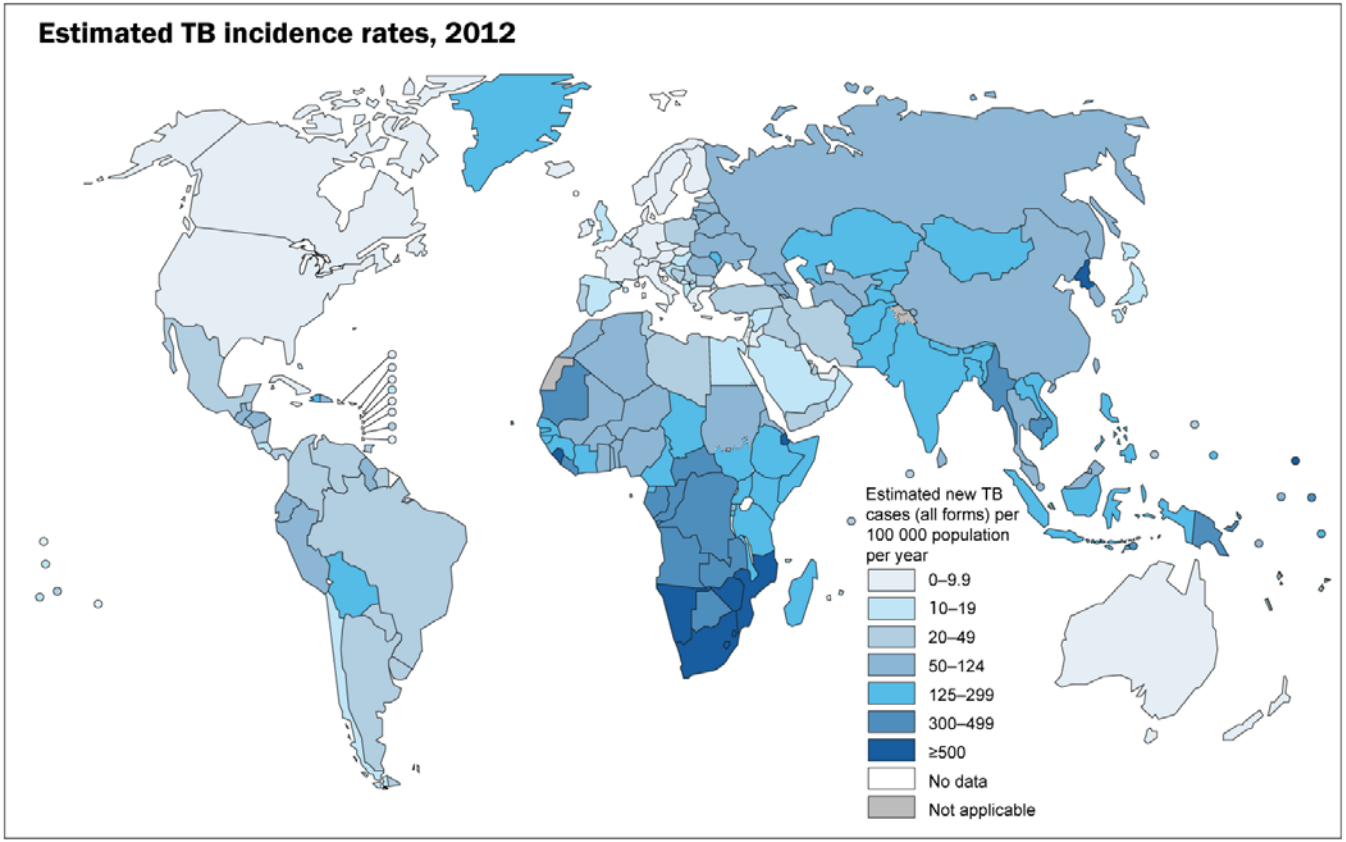


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organisation concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximated border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organisation

World Health Organization

Figure 2: Global Prevalence of Malaria according to WHO in 2012 [10].



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2013*. WHO, 2013.

World Health Organization

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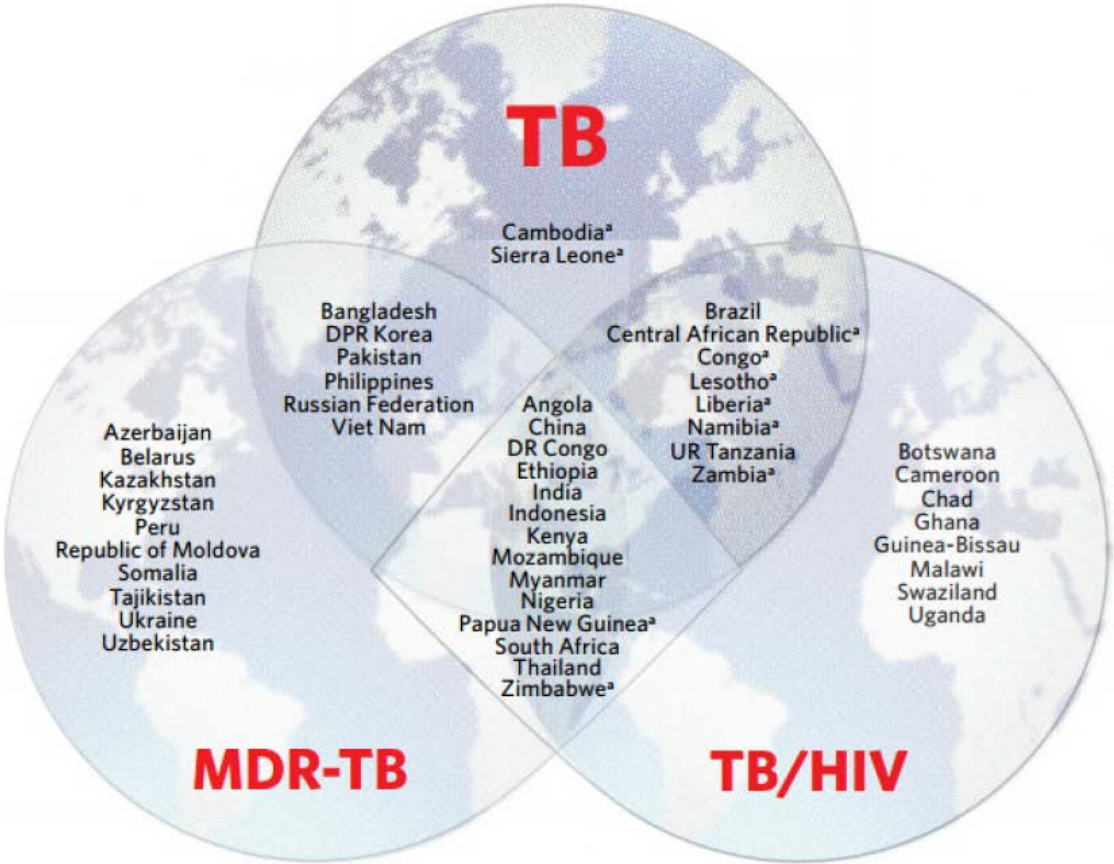
Countries in the three TB high-burden country lists that will be used by WHO during the period 2016–2020, and their areas of overlap



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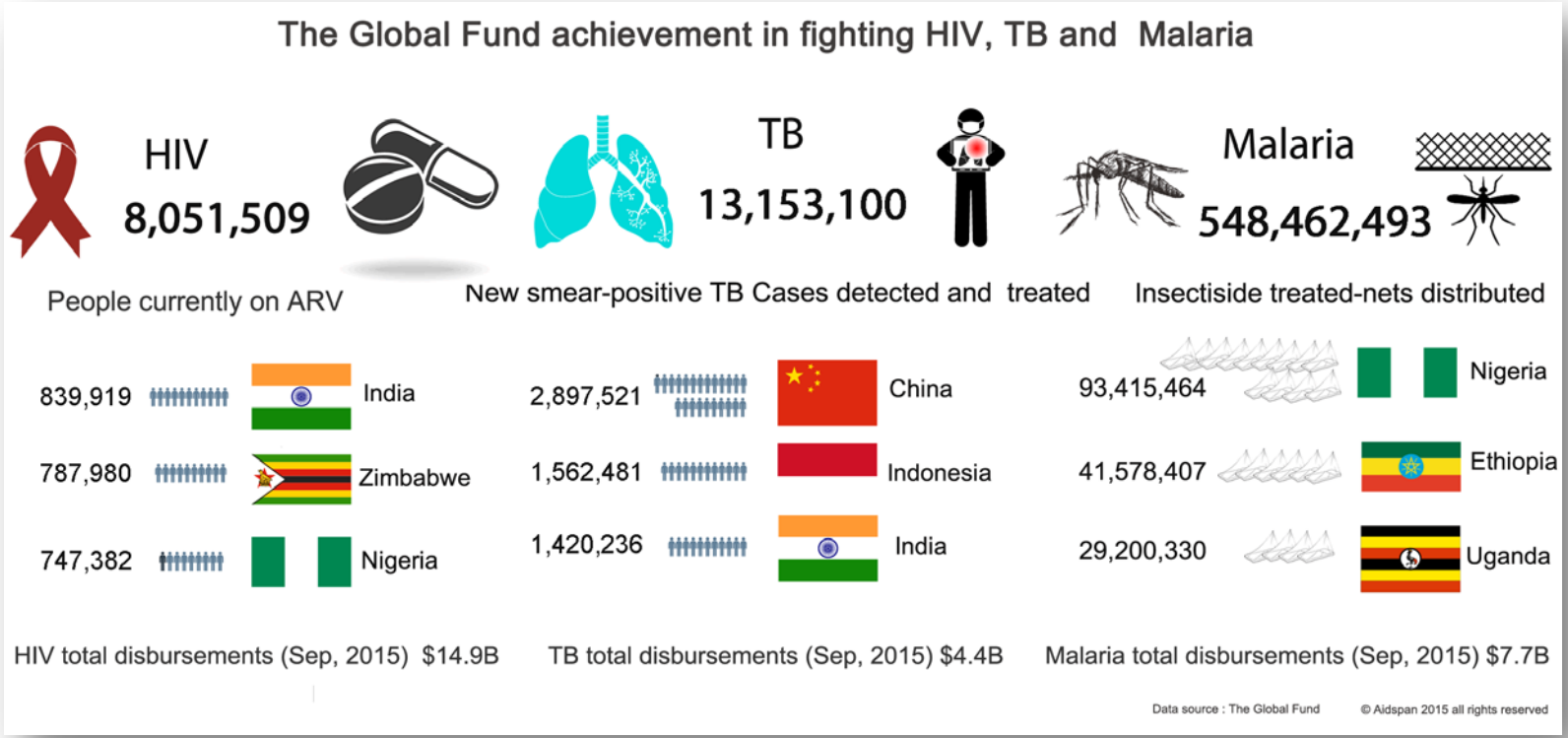

Prescription Drug Spending Hits Record $425 Billion in U.S.

Bloomberg, April 2016

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The Value of Vaccines in Disease Prevention

KEY POINTS

- ✓ According to the World Health Organization (WHO), immunizations save an estimated 2.5 million lives every year.
- ✓ For every $1 the U.S. spends on childhood vaccinations, we save $10.20 in disease treatment costs.
- ✓ In the U.S., vaccine use saves $13.5 billion in direct costs.

Pfizer (2017). The Value of Vaccines. https://www.pfizer.com/files/health/VOMPaper_Vaccines_R7.pdf

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Impact of Vaccines on Infectious Disease Morbidity in the U.S.

	Pre-vaccine Era Estimated Annual Morbidity in the US*	Most Recent Reports of Cases in the US†	% Decrease
Diphtheria	21,053	0	100%
H. Influenzae	20,000	243	99%
Measles	530,217	61	99%
Mumps	162,344	982	99%
Pertussis	200,752	13,506	93%
Polio	16,316	0	100%
Rubella	47,745	4	99%
Congenital Rubella	152	1	99%
Varicella	4,085,120	449,363	89%

Pfizer (2017). The Value of Vaccines. https://www.pfizer.com/files/health/VOMPaper_Vaccines_R7.pdf

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Which states have the lowest vaccination rates?

Meanwhile, the study found that Colorado and Arkansas had the lowest vaccination rates for the conditions. Specifically, the states with lowest MMR vaccination rates were:

1. Colorado (85.7%);
2. Arkansas (85.9%); **2017 – (87%)**
3. Pennsylvania (87%);
4. Idaho (89%); and
5. North Dakota (89.9%).

Source: CDC report August 2013

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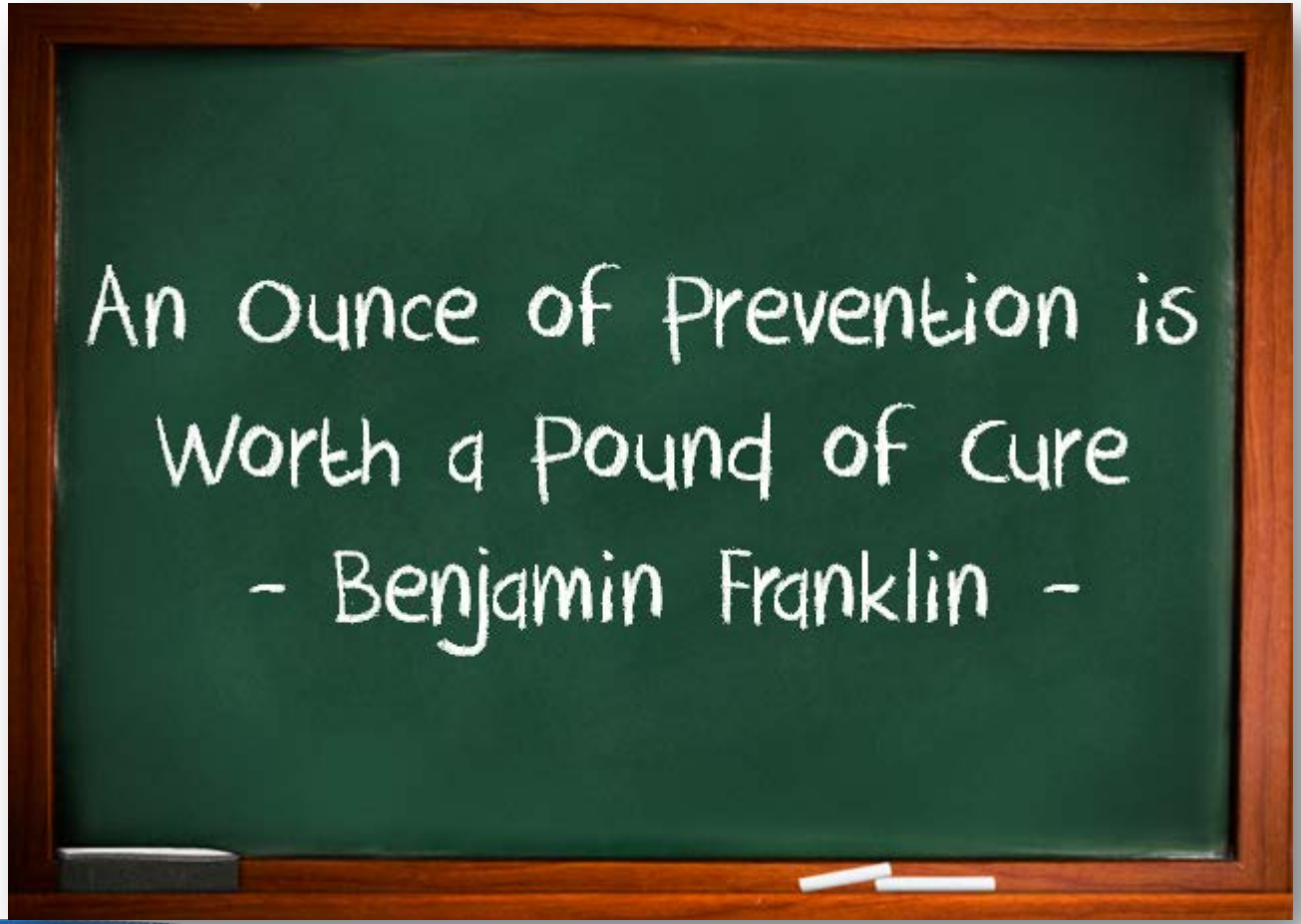

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"The Next Seven Great Achievements in Pediatric Research"

(Cheng TL, et al. Pediatrics. April 21, 2017, https://doi.org/10.1542/peds.2016-3803).

The authors, who include COPR Chair Clifford W. Bogue, M.D., FAAP, predict the following achievements:

1. More pediatric immunizations prevent emerging and persistent diseases.
2. Cancer immunotherapy in pediatrics shows promise.
3. Genomic discoveries predict, prevent and more effectively treat disease.
4. Big life-course data recognize fetal and childhood origins of adult health and disease resulting in effective early interventions.
5. Knowledge of the interaction of biology and the physical and social Environment leads to effective prevention for individual and population health.
6. Quality improvement science creates safe, efficient systems of care.
7. Implementation and dissemination research reduces global poverty.

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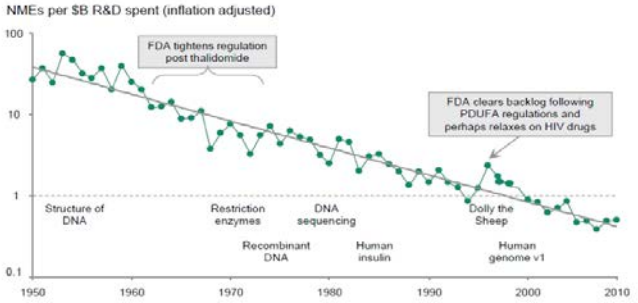
Pharma Industry Undergoing Dramatic Transformation

R&D productivity is on the decline



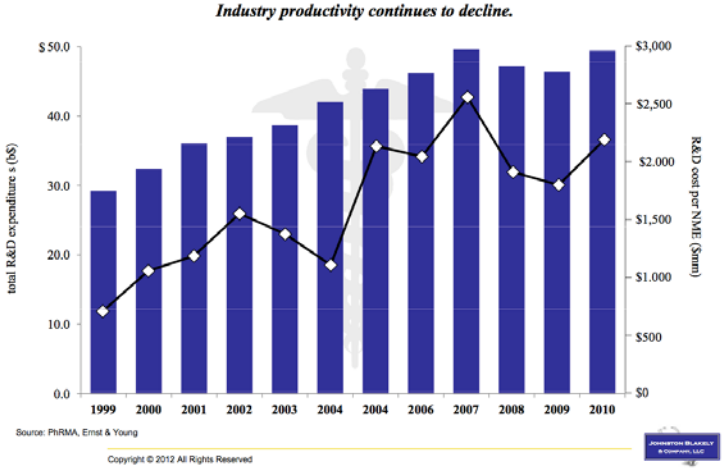


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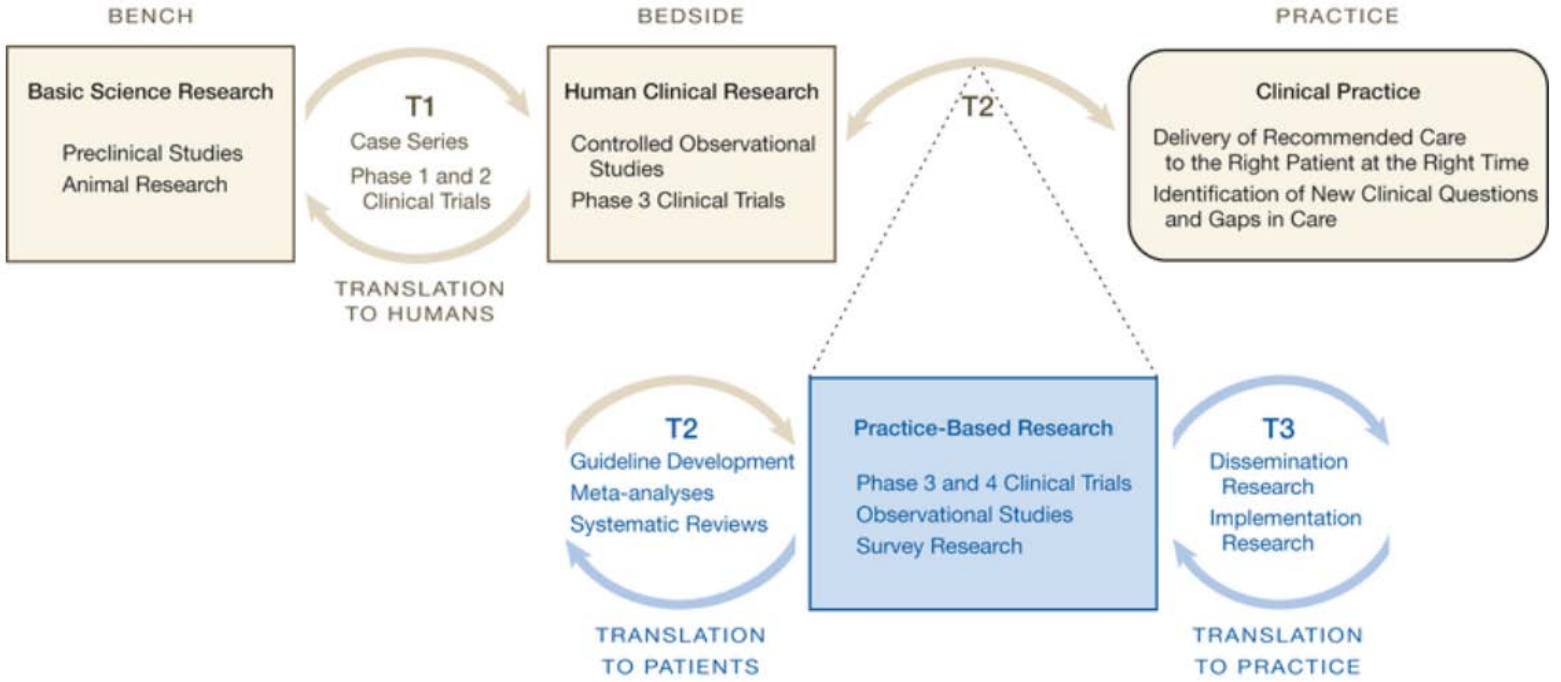
Figure. "Blue Highways" on the NIH Roadmap



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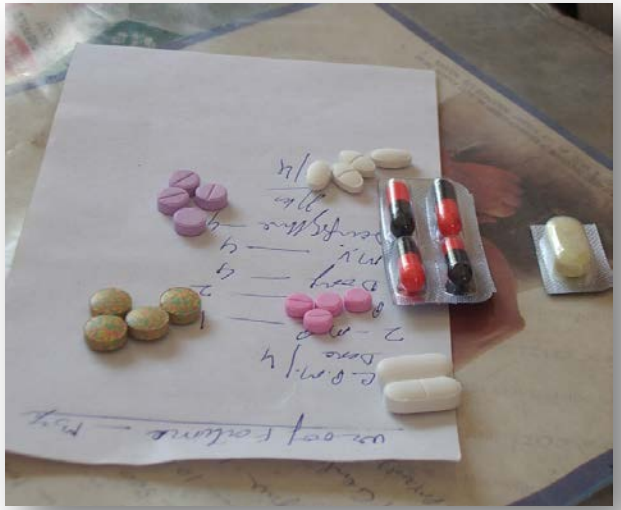
In a rural health clinic, somewhere in India, a women with a sick child …..

..and these are the medicines which were given to the child



Photograph: Noël Cranswick, 2006

Courtesy of Dr. H. Hogerzeil, June 2008

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WHO Revised Pediatric TB Dosing Guidelines

Recommended Dose (Range)	10 mg/kg (10-15)	15 mg/kg (10-20)	35 mg/kg (31-40)
Weight in Kg	**150 mg pill Isoniazid mg/Kg**	**200 mg pill Rifampin mg/Kg**	**400 mg pill Pyrazinamide mg/Kg**
5 (1/2 pill)	15	20	40
8 (1.2 pill)	9.4	12.5	25
10 (1 pill)	15	20	40
15 (1 pill)	10	13.3	26.6
20 (1.5 pills)	11.2	15	30
25 (2 pills)	12	16	32
30 (2 pills)	10	13.3	26.6

WHO Pediatric TB Dosing Guidelines; 2009

Evaluation of the Adequacy of the 2010 Revised World Health Organization Recommended Dosages of the First-line Antituberculosis Drugs for Children: Adequacy of Revised Dosages of TB Drugs for Children.

Yang H et. al. Pediatr Infect Dis J. 2018 Jan;37(1):43-51.

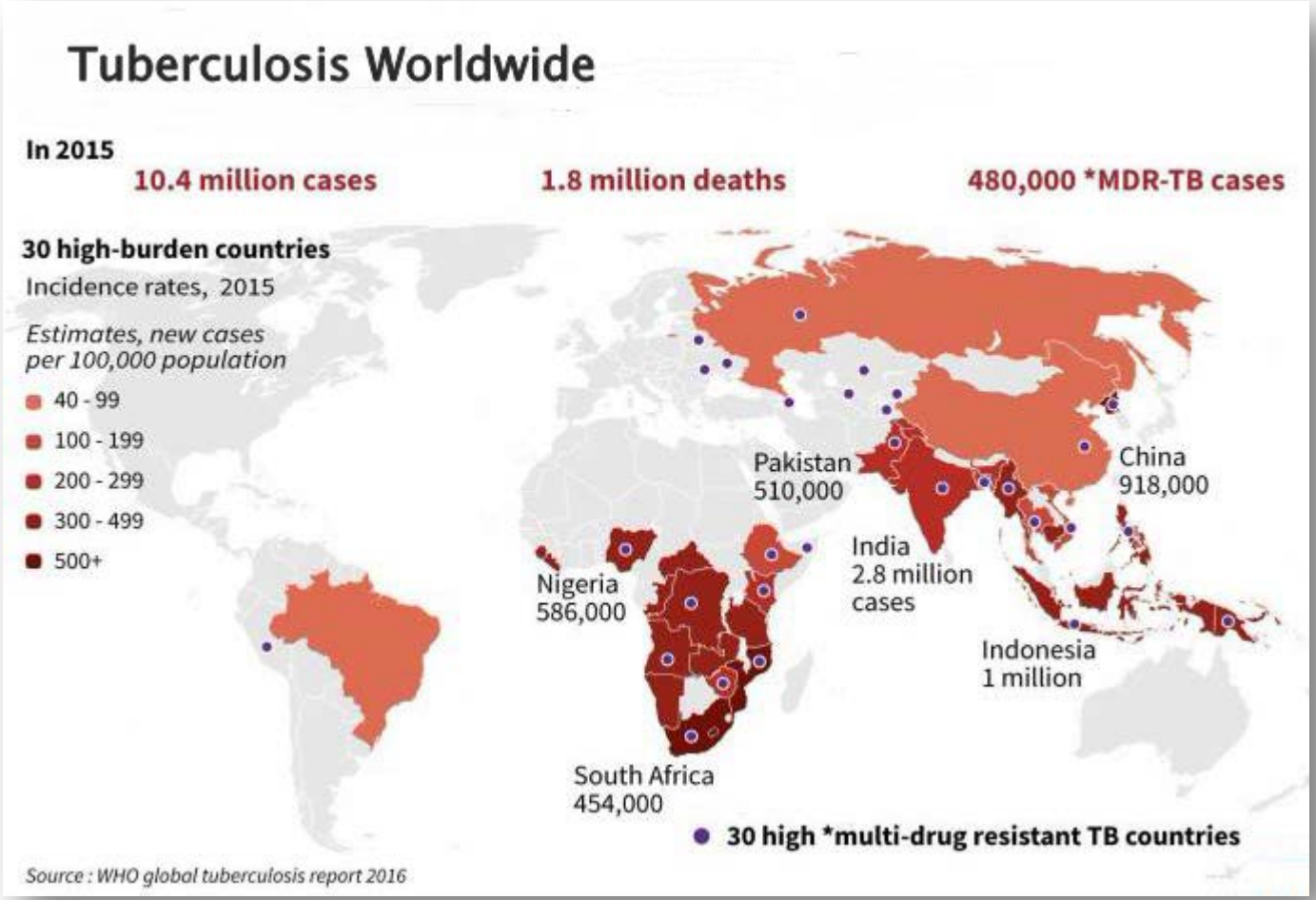
RESULTS:

Of the 100 children, 58% were male, 50% HIV-infected and 49% younger than 5 years old. Low Cmax occurred in 9/100 (9.0%), 61/100 (61.0%), 17/97 (17.5%) and 60/97 (61.9%) for isoniazid, rifampin, pyrazinamide and ethambutol, respectively…. Factors associated with low Cmax were NAT2 metabolizer phenotype status for isoniazid; height, dosage and HIV coinfection status for rifampin; height for pyrazinamide; and age, dosage and HIV coinfection status for ethambutol.

CONCLUSIONS:

The high frequency of low rifampin and ethambutol Cmax in our study is consistent with emerging pharmacokinetic data in children treated according to the new WHO recommendations. Higher dosages than currently recommended especially for rifampin may be necessary in children.

Tuberculosis Worldwide



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The need for rational selection: New essential drugs are expensive

Antibiotics for gonorrhoea:	50-90x price of penicillins
Antimalarial drugs:	chloroquine $0.10 per treatment artemether-lumefantrine $2/pp (20x) atavaquone-proguanil $40/pp (400x)
Antituberculosis:	$15 for DOTS vs $300 for MDR (20x)
Antiretrovirals:	$100/year for 1st-line medicines; but $2000-$3000 (20-30x) for 2nd-line ARVsin

From Dr. Hans Hogerzeil 2008

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A New Colonialism? — Conducting Clinical Trials in India

Samiran Nundy, M.Chir., and Chandra M. Gulhati, M.D., D.T.M.&H.

A Private, "One-Man" Clinic in New Delhi Where Letrozole Was Tested.

N Engl J Med 2005;352:1633-36

"Too many researchers fail to declare conflicts of interest, and it is only too easy to buy up poor illiterate patients, who are unable to give truly informed consent, and recruit them to trials which are of little or no benefit to them and which fail to safeguard their interests," he said.

(Courtesy of Prof. M. Bonati, 2005)

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Agent B

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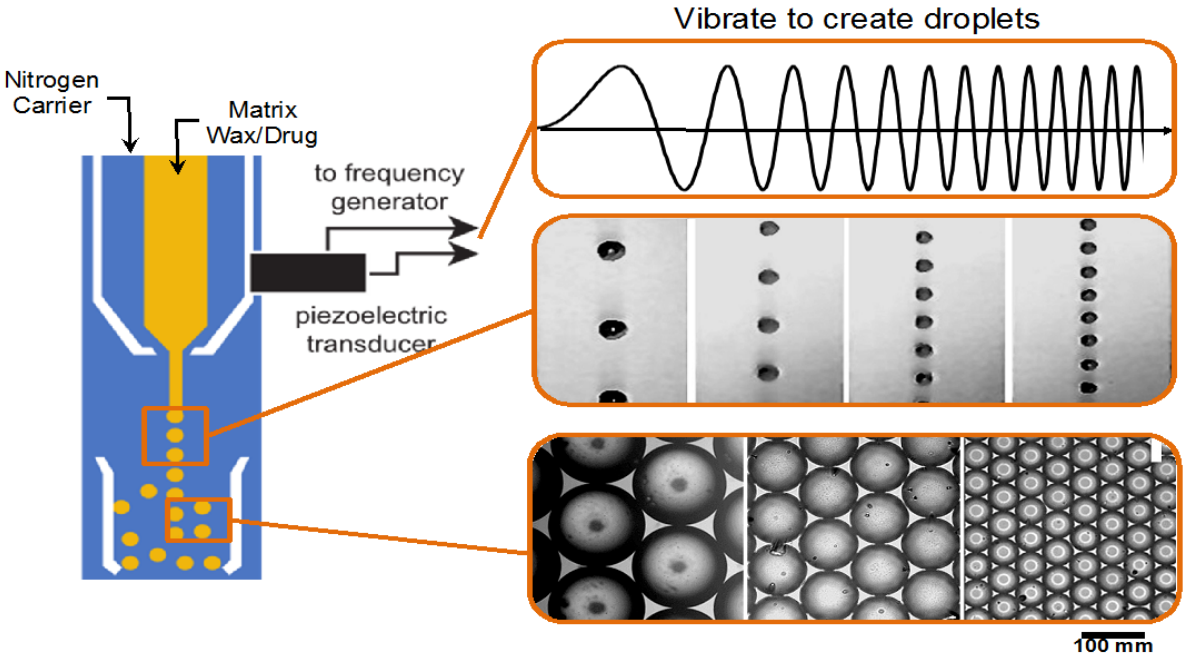
Orbis Biosciences Microsphere Production



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Characteristics of Study Population…..

	Randomization Sequence[a]				
	I (n=5)	II (n=7)	III (n=6)	IV (n=6)	P value[b]
Gender, n (%)					0.08
Male	3 (60%)	6 (85.7%)	1 (16.7%)	2 (33.3%)	
Female	2 (40%)	1 (14.3%)	5 (83.3%)	4 (66.7%)	
Race, n (%)					0.71
White	5 (100%)	7 (100%)	5 (83.3%)	6 (100%)	
African American	0	0	1 (16.7%)	0	
Ethnicity, n (%)					-
Not Hispanic or Latino	5 (100%)	7 (100%)	6 (100%)	6 (100%)	
Age (years), mean (SD)	18.6 (0.9)	19.9 (1.7)	20 (3.5)	20.8 (2.2)	0.48
Height (cm), mean (SD)	178.9 (9)	180.4 (7.1)	166.4 (11.2)	174.3 (7.4)	0.05
Weight (kg) , mean (SD)	77.5 (12.6)	79.2 (14.8)	62 (10.8)	71.9 (11.7)	0.11

[a] I: Reference, Control, Test 5 min., Test 24 hr; II: Test 24 hr., Test 5 min., Control, Reference; III: Test 5 min., Test 24 hr., Reference, Control; IV: Control, Reference, Test 24 hr., Test 5 min.
[b] P values are from Fisher's exact test for categorical variables and one-way ANOVA for continuous variables.

Bai S, et al. *J Pharm Pharmacol* 2017;69:489-496

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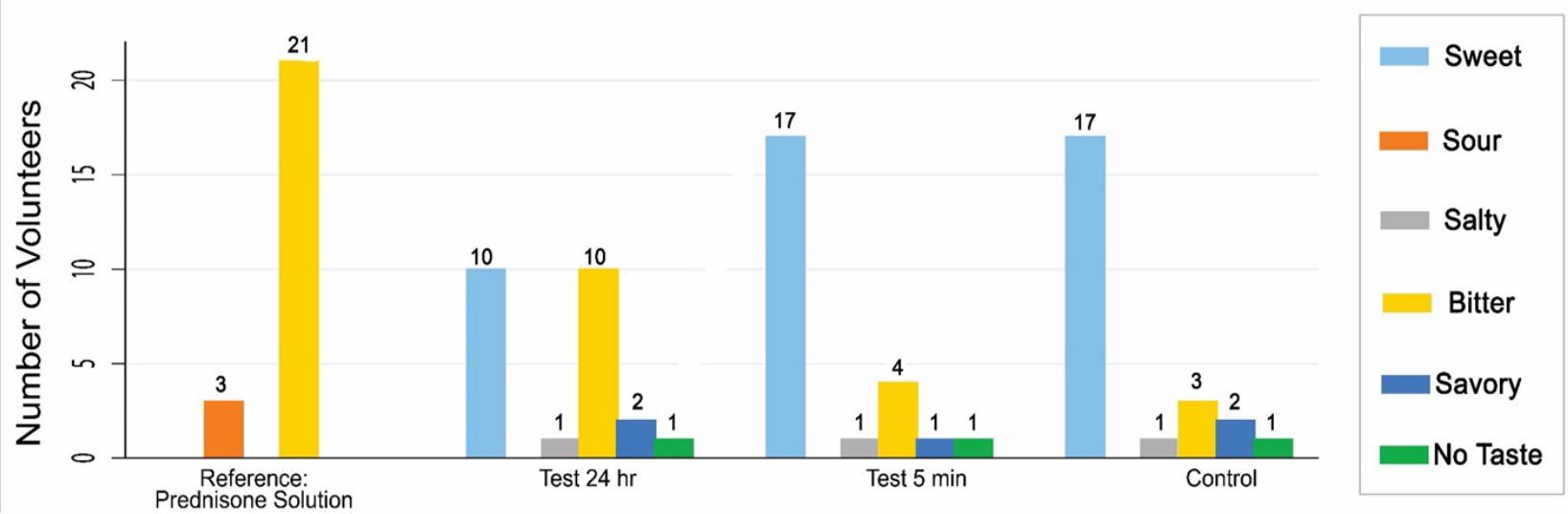
Description of Taste for Two Prednisone Formulations



(Test = microsphere prednisone formulation)

Bai S, et al. *J Pharm Pharmacol* 2017;69:489-496

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Before Intake Test

Questionnaire

To be filled out by the investigator	NAME_____ DATE_____ SUBJECT ID_____ PRODUCT ID_____

This questionnaire is designed to rate how much you did or did not enjoy the product. For each of the question below please check one of the blue squares. After the initial taste question please circle the word that best describes the type of taste of the product. Finally, please rate your likeliness of taking the product if prescribed.

*What did you think of the **taste**?*

Dislike Extremely	Dislike Very Much	Dislike Moderately	Dislike Slightly	Neither Like nor Dislike	Like Slightly	Like Moderately	Like Very Much	Like Extremely
☐	☐	☐	☐	☐	☐	☐	☐	☐

Circle one word that best describes the initial taste:

Sweet Sour Salty Bitter Savory No Taste

*What did you think of the **texture/mouth feel**?*

Dislike Extremely	Dislike Very Much	Dislike Moderately	Dislike Slightly	Neither Like nor Dislike	Like Slightly	Like Moderately	Like Very Much	Like Extremely
☐	☐	☐	☐	☐	☐	☐	☐	☐

*What did you think of the **smell**?*

Dislike Extremely	Dislike Very Much	Dislike Moderately	Dislike Slightly	Neither Like nor Dislike	Like Slightly	Like Moderately	Like Very Much	Like Extremely
☐	☐	☐	☐	☐	☐	☐	☐	☐

Do you have any comments about this product?

*(Five minutes after test) What did you think of the **after taste**?*

Dislike Extremely	Dislike Very Much	Dislike Moderately	Dislike Slightly	Neither Like nor Dislike	Like Slightly	Like Moderately	Like Very Much	Like Extremely
☐	☐	☐	☐	☐	☐	☐	☐	☐

Would you be willing to take this product if prescribed?

Extremely Unlikely	Very Much Unlikely	Moderately Unlikely	Slightly Unlikely	No Preference	Slightly Likely	Moderately Likely	Very Much Likely	Extremely Likely
☐	☐	☐	☐	☐	☐	☐	☐	☐

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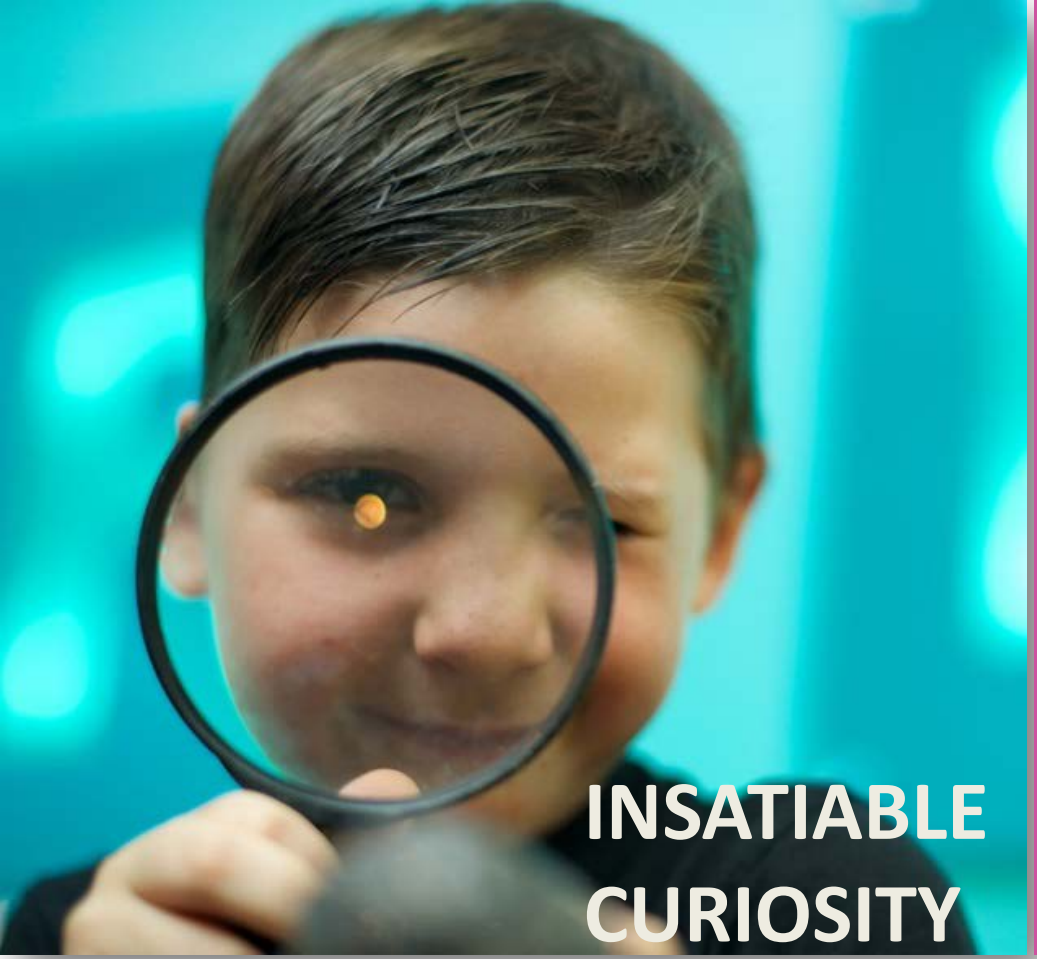

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COMPASSION

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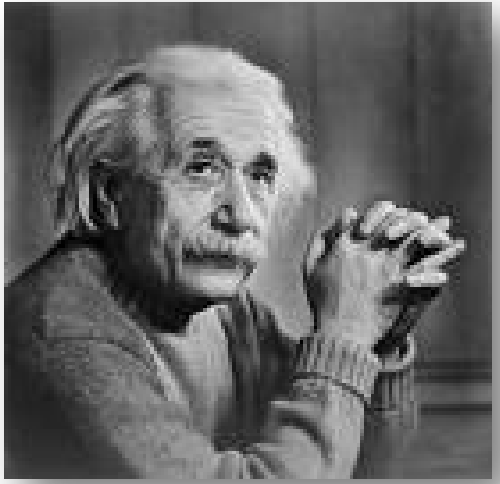

"We can't solve problems by using the same kind of thinking we used when we created them."

"Imagination is more important than knowledge"

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It’s all y’all’s responsibility

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CHARLES SHAW
Cabernet Sauvignon
Merlot
In 2004, a $1.99 bottle of wine, "Two Buck Chuck", beat 2300 other wines to win the 28th Annual International Eastern Wine Competition.
KickassFacts.com

- Ross and Mary Whipple Family
- Marcy Doderer, FACHE
- Richard F. Jacobs, MD
- J. Steven Leeder, PharmD, PhD
- All of my collaborators
- Barry Brady, MSc, FACHE
- Ms. Jenny Kubacak
- The staff of ACRI