CARRA

Childhood Arthritis and Rheumatology Research Alliance

PJIA safety assessment considerations

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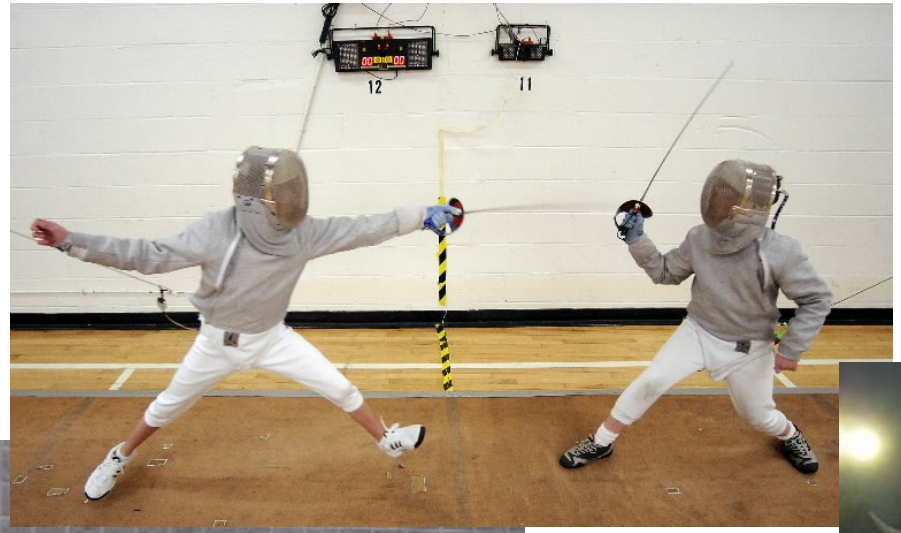
JIA Patients on Biologics



But are they *safe in children*?

ARE THEY SAFE DURING TREATMENT?

DO THEY IMPACT DEVELOPMENT?

ARE THEY SAFE IN THE FUTURE?

ARE THEY SAFE DURING TREATMENT?

Safety studies must be performed **IN CHILDREN**

- Children are not just small adults
- Children have lower baseline risks
  Infection
  Malignancy
  Most everything!
- Children have less comorbidities
- Children have less concomitant medications
- Children are basically healthier
- Children are still developing

Phase 3 studies do not adequately determine safety

- Analysis of 71 adalimumab clinical trials (3 JIA)
- Total of 23, 458 patients (212 JIA)
- 36,730 patient years (605 JIA)
- Randomized withdrawal design exposes ALL JIA patients to study drug

Table 2 Incidence rates of serious adverse events of interest*

	Rheumatoid arthritis	Juvenile idiopathic arthritis	Ankylosing spondylitis	Psoriatic arthritis	Psoriasis	Crohn's disease
N	14 109	212	1684	837	3010	3606
Exposure, PYs	23 942.6	604.9	1985.6	997.5	5061.8	4138.0
Serious infections	4.6	2.0	1.4	2.8	1.7	6.7
Active tuberculosis	0.3	0	0	0.2	0.1	<0.1
Opportunistic infections	<0.1	0	0	0	0	<0.1
Demyelinating disorder	<0.1	0	<0.1	0	0	0.1
Lupus-like syndrome	<0.1	0	0.1	0	0	<0.1
CHF	0.2	0	0.1	0	<0.1	0
New onset/worsening of psoriasis	<0.1	0	<0.1	0.1	<0.1	<0.1
Malignancies excluding lymphoma and NMSC	0.9	0	0.2	0.2	0.6	0.5
Lymphoma	0.1	0	<0.1	0.2	<0.1	<0.1
NMSC†	0.2	0	0.3	0.1	0.1	<0.1
Melanoma	<0.1	0	<0.1	0	0.2	0
Any AE leading to death	0.8	0	<0.1	0.3	0.2	0.1

*Rates in events/100 PYs.
†Only serious NMSC events.
AE, adverse event; CHF, congestive heart failure; NMSC, non-melanoma skin cancer; PYs, patient-years.

Burmester, et al. Ann Rheum Dis 2013

Safety events we care about are uncommon

- Hospitalized infection rates in children with JIA
  - 1-3 per 100 person-years of exposure to TNFi
  - For 80% power to detect a *doubling of risk*, need sample size of **>1000 person-years** of exposure to study drug and comparator
- Malignancy rates in childhood
  - 2 per 10,000 person-years during childhood
  - For 80% power to detect a *doubling of risk*, need sample size of **>100,000 person-years** of exposure to study drug and comparator
  - For 80% power to detect *5-fold increased risk*, need sample size of **>15,000 person-years** of exposure to study drug and comparator

Long Term Safety

DO THEY IMPACT DEVELOPMENT?

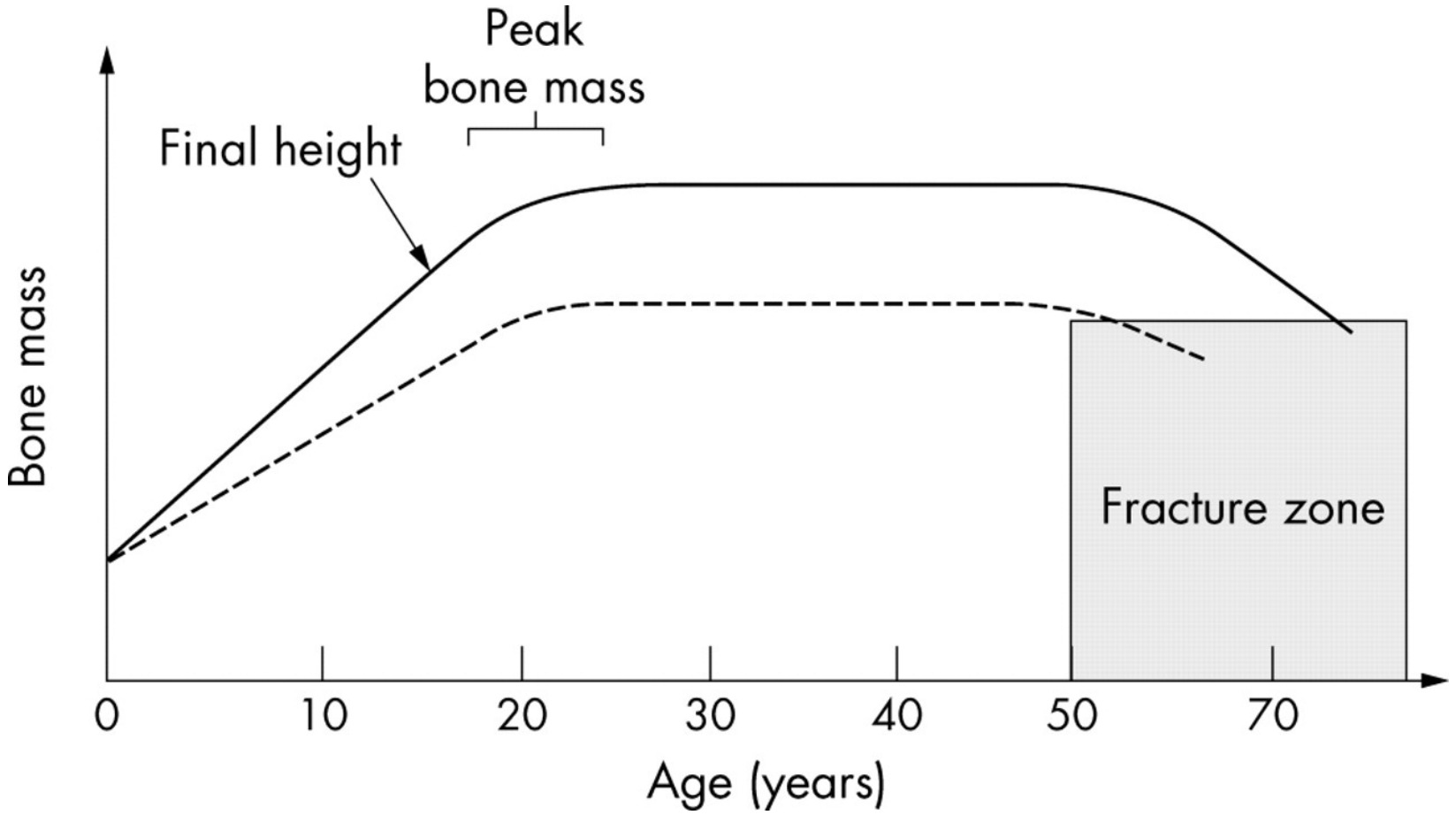
ARE THEY SAFE IN THE FUTURE?

What is effect of drugs on immature systems?

- Growth and bone health
- Puberty and future reproductive health
- Immune system development
- Risk of malignancy
- Central nervous system development
- Cardiovascular risk
- Microbiome

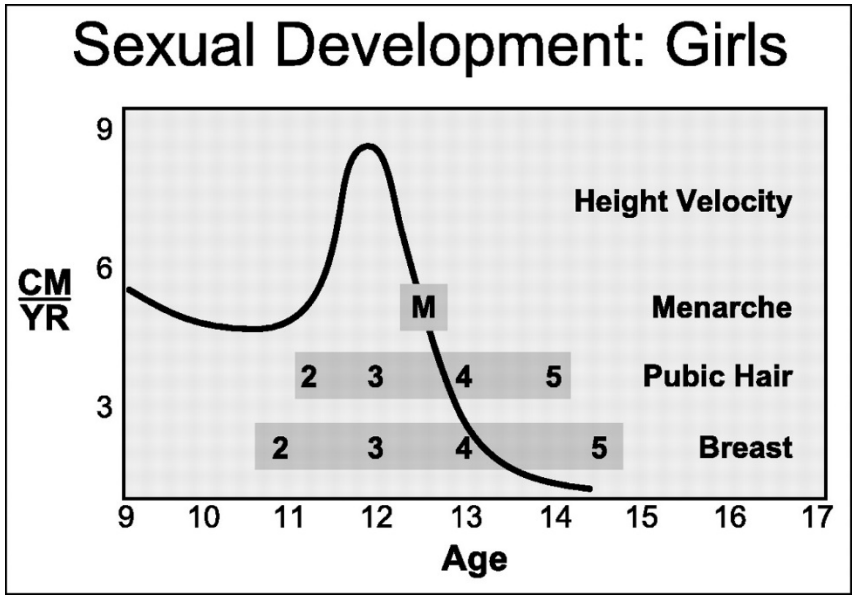
Growth and Bone Health

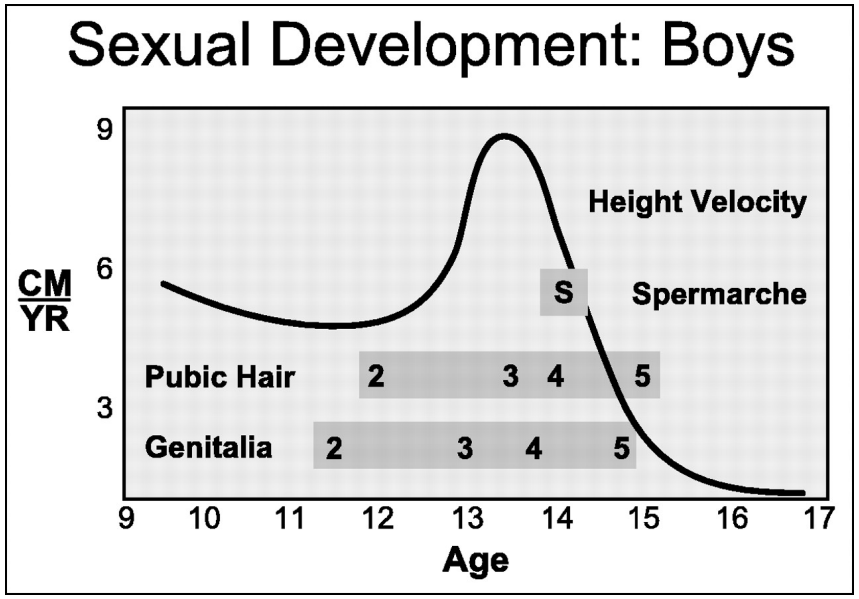
- Majority of bone deposited in adolescence
- Peak bone mass achieved around 20 yrs of age
- Perturbation in PBM during childhood may lead to early osteoporosis and increased fractures



Davies Arch Dis Child 2005

Puberty and Reproduction

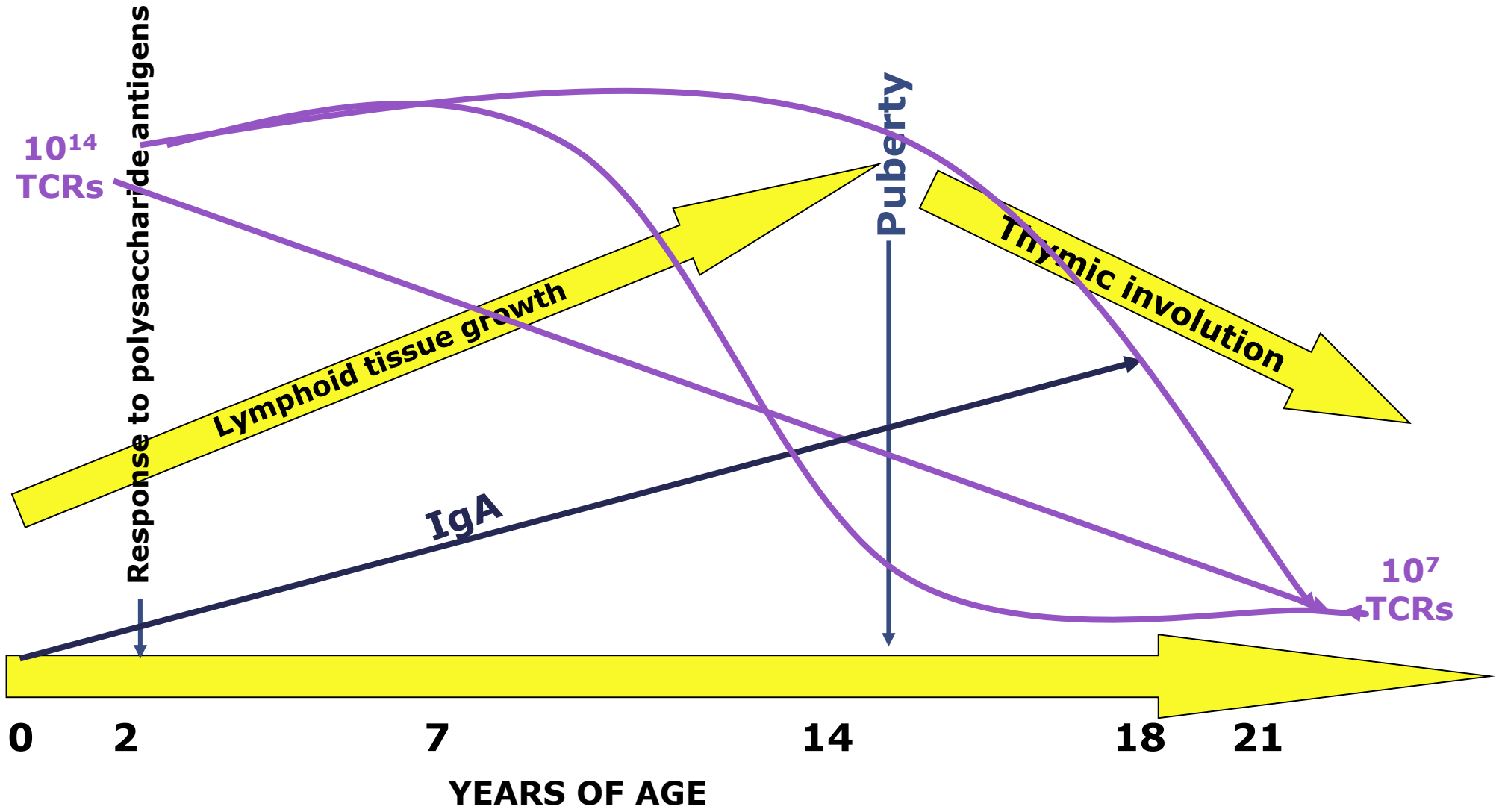




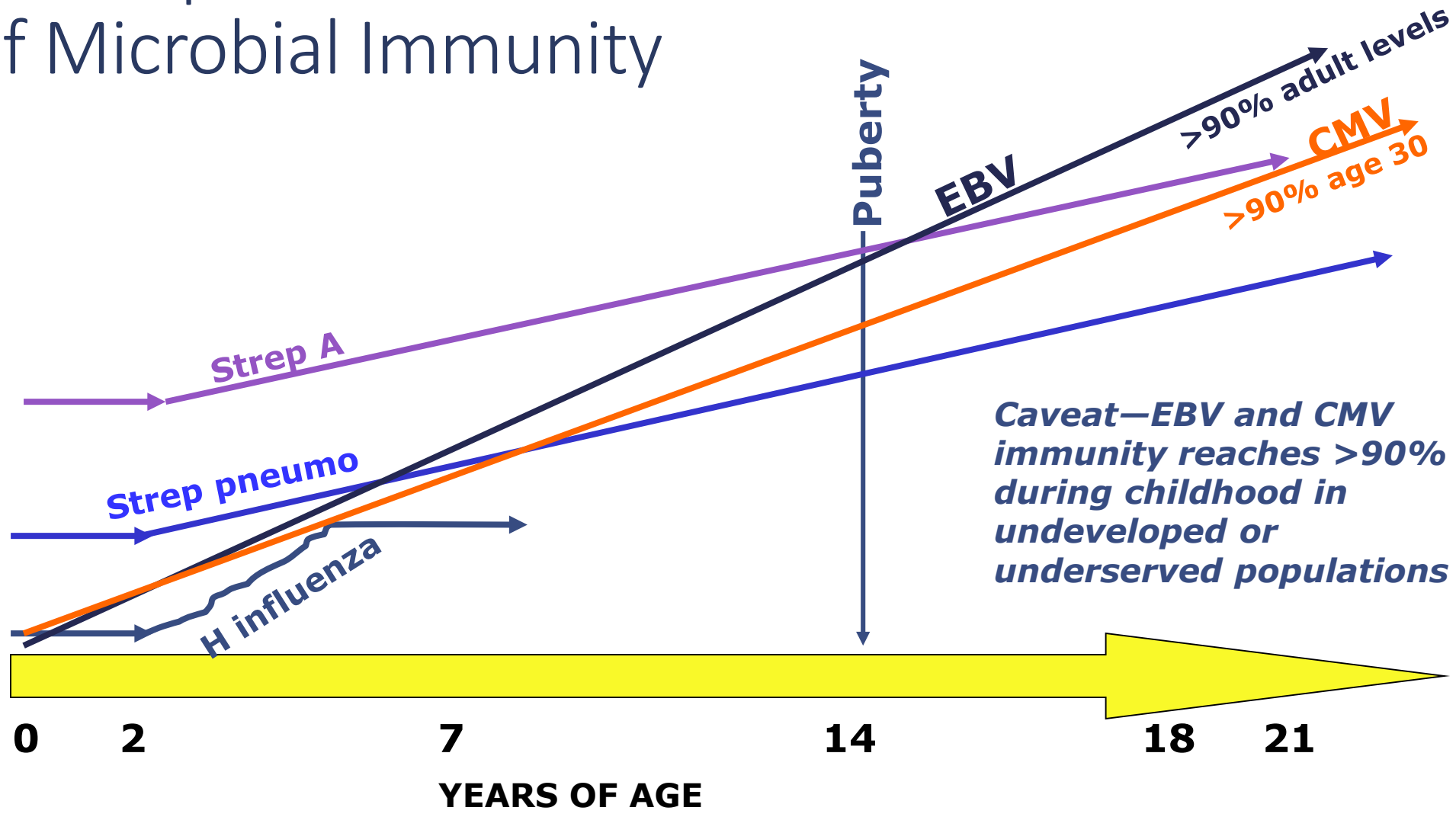
- Adrenal and gonadal axis maturation not complete until late adolescence
- Gonadal hormones impact brain development
- Perturbation can have far ranging physical and psychological consequences

Rosen Pediatrics in Rev 2004
Shultz Neuro Sci Biobev Rev 2016

Immunologic Development

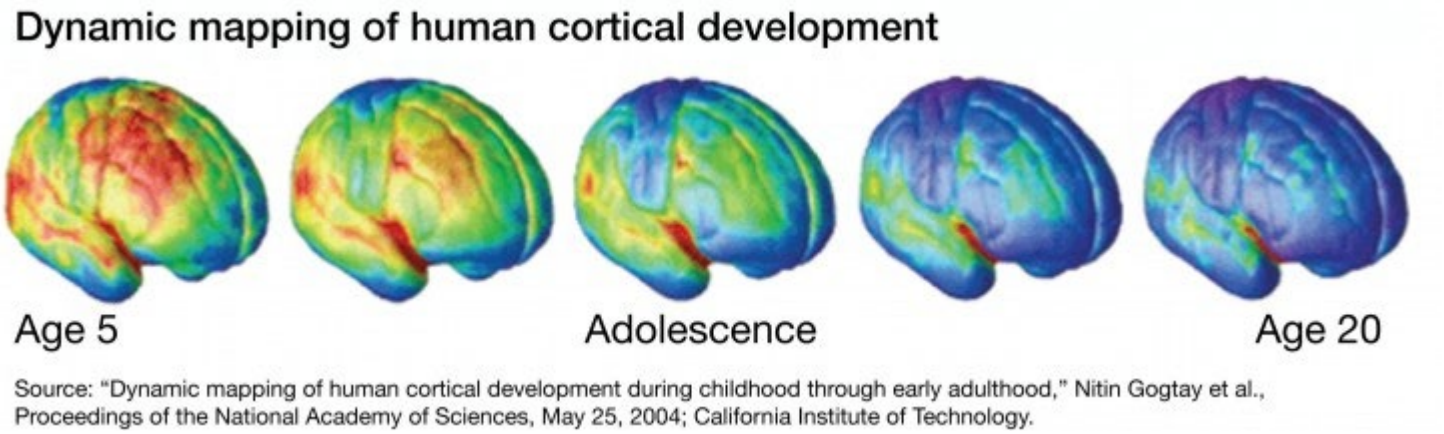


Development of Microbial Immunity

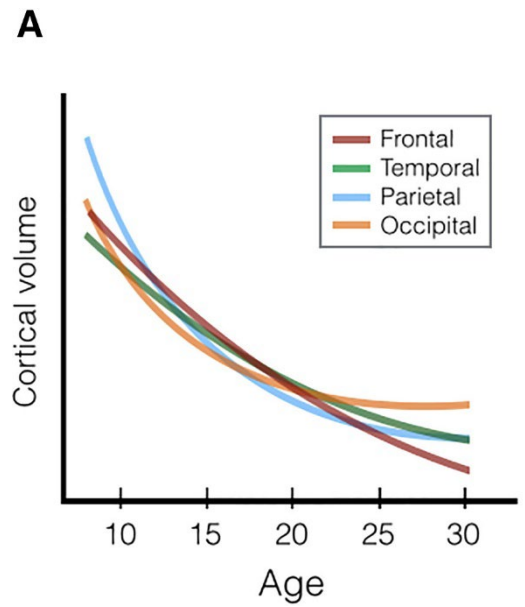


Neurologic Development

- Gray matter peaks around 10-12 yrs
- Frontal lobes not fully developed until 25-30 yrs
- Communication between distant brain regions not present until adulthood



Source: "Dynamic mapping of human cortical development during childhood through early adulthood," Nitin Gogtay et al., Proceedings of the National Academy of Sciences, May 25, 2004; California Institute of Technology.



Gogtay, PNAS 2004
Somerville, Neuron 2016

HOW DO WE DEAL WITH THESE ISSUES?

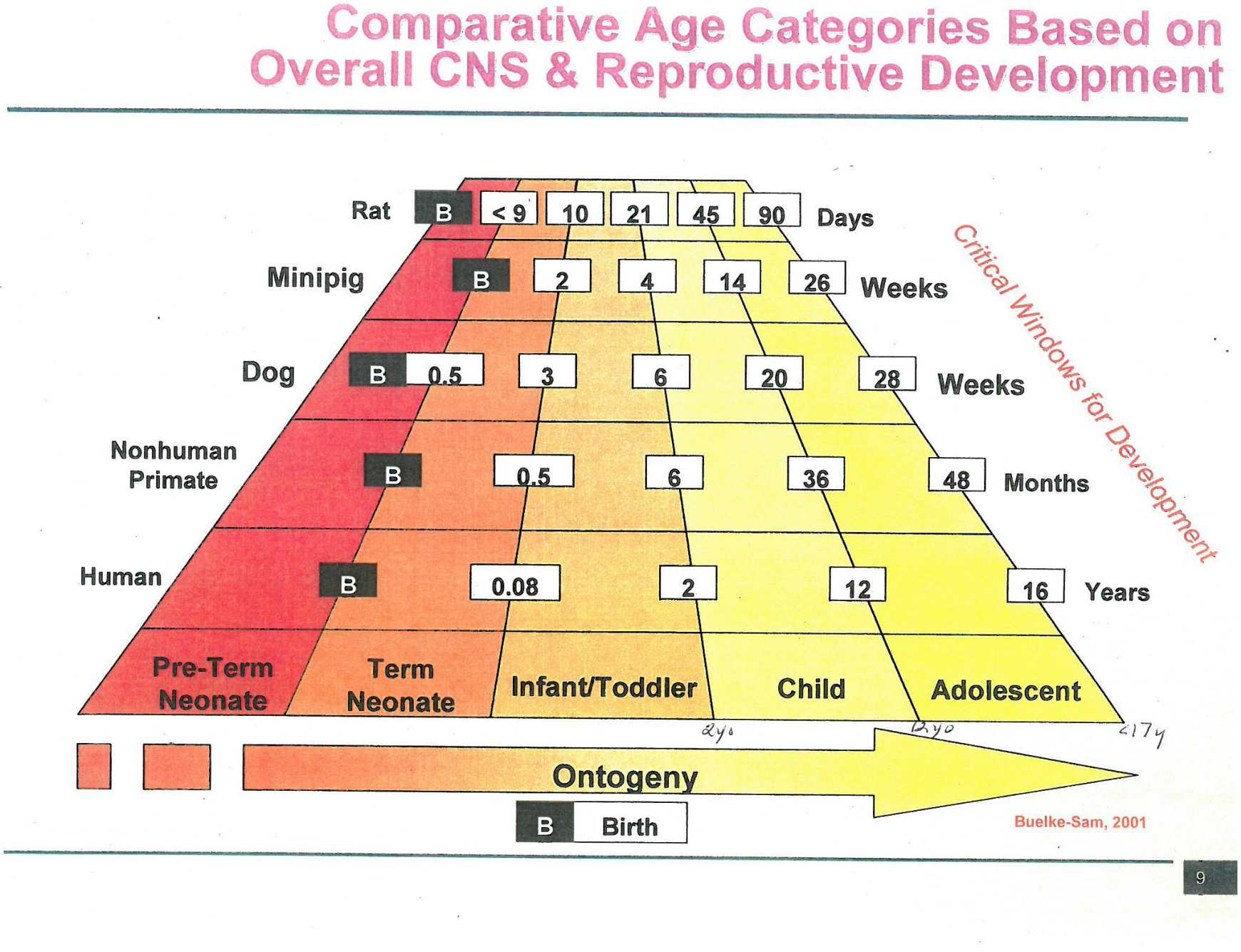
Approaches

Preclinical animal studies

Clinical trials

Real world data sources post marketing

- Registries
  - Drug based
  - Disease based
  - SAE based (ie tumor registry)
- Claims data
- EHR



Safety assessment starts with robust juvenile animal data

- Age appropriate
- System appropriate
- Findings used to identify potential issues in children
- Target human pediatric safety studies

Disease vs Drug Based Safety Registries

DRUG BASED REGISTRIES

- Dynamic and complex use of medication in clinical practice
- Limited numbers of adequate comparator patients
- Sample size and duration of follow-up inadequate

DISEASE BASED REGISTRIES

- Abundance of comparators
- Capture new medication use after enrollment
- Closer approximation to “real-world” use
- Accurate estimates of incidence of new medication use

Challenges Assessing Malignancy Risk

- Few events
- Confounding by disease severity
- Treatment with multiple medications
- Unknown risk window

Study of U.S. Administrative Claims Data

- Billing records identified children with JIA, IBD, PsO; their medication use; and diagnosis of malignancy.
- Malignancy outcome algorithm highly consistent with results expected from cancer registry (SIR 0.97 [0.91-1.05]).
- Claims data currently being used for postmarketing pharmacoepi study assessing long-term safety of denosumab

Cohort	# Cancers	P-Yrs Follow-up	Rate per 1000 p-yrs	SIR [95% CI]
JIA No TNFi Use	13	39,257	0.33	2.1 [1.1-3.5]
JIA TNFi Use	8	16,272	0.49	3.1 [1.3-6.1]
JIA + IBD + PsO No TNFi Use	42	121,801	0.35	2.1 [1.5-2.9]
JIA + IBD + PsO TNFi Use	15	30,703	0.49	2.9 [1.6-4.9]

Beukelman, Ann Rheum Dis 2018
Xue, Pharmacoepidemiol Drug Saf. 2013

Current Issues in Disease Registry Safety Studies

- Extensive inclusion/exclusion criteria for cohorts
- Patients not contributing data to both the comparator and study drug cohorts
- Inappropriate selection of comparators
- Long delays from label approval to start of phase IV studies
- Unrealistic enrollment targets for new second and third line agents

Possible Solutions

- Conduct Phase IV studies using disease-based registries and other real work data sources
- Plan with companies to begin Phase IV registries immediately after pediatric label approval to capture backlog of patients starting new drug
- Include all patients who newly initiate drug of interest are in cohort
- Select appropriate comparator cohort(s) at time of analyses/data transfer
- Define study by duration (e.g., capturing all patients initiating drug over 15 years) rather than number of persons

Summary

- Safety is probably different in kids due to comorbidities, etc. (including the possibility that the drugs are actually safer in kids!)
- Pediatric-specific issues like immune development can only be studied in kids.
- The safety issues we are most concerned about are rare or very rare, so we need to study as many kids as possible for as long as possible.
- We are going to have to continue to accept limited safety information at the time of approval.
- Robust post marketing real world data sources, such as disease-based registries, will provide the most useful long-term safety data.

CARRA

Thank you!

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