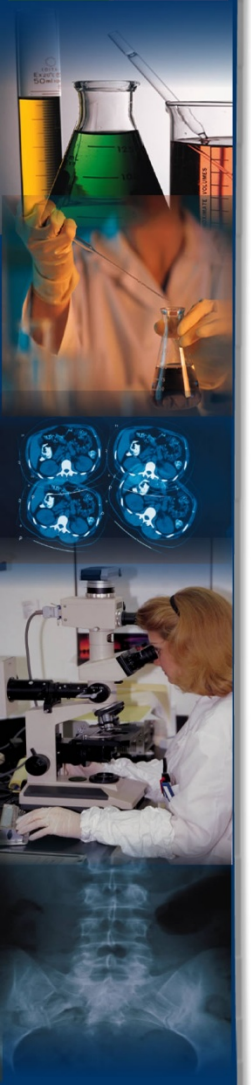

U.S. Vaccine Markets: Characteristics, Cases, and Controversies

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Book Forum -- American Enterprise Institute
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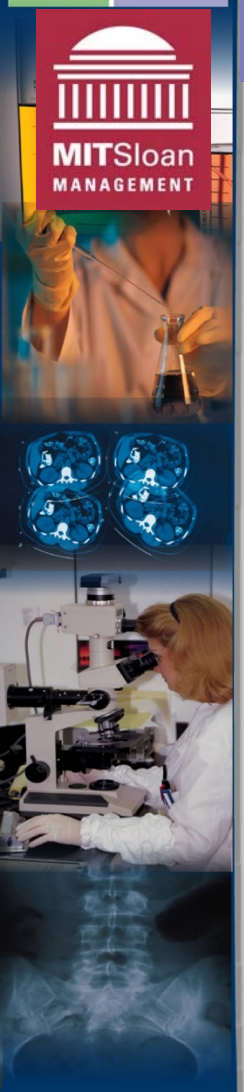
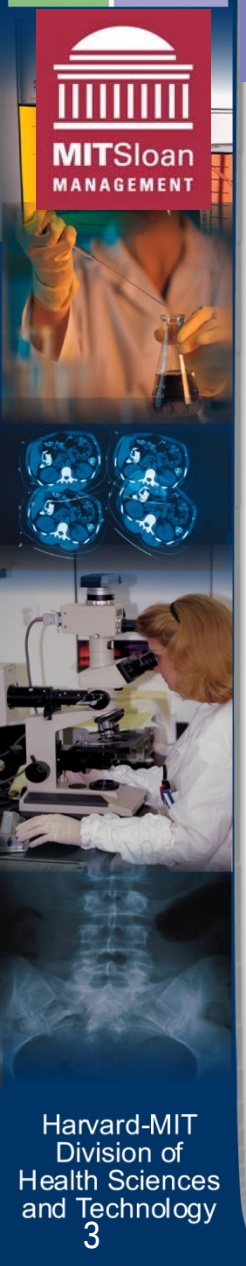
Any opinions expressed are those of the authors.

Harvard-MIT Division of Health Sciences and Technology



Focus of Book

- Compare vaccines, other biologics (derived from living organisms) and traditional small molecule pharmaceuticals (chemically synthesized) through the entire product life cycle from discovery and IP to post-launch surveillance
- Illustrate in detail with four case studies
- Trace history and recent developments regarding association between MMR vaccinations and autism



"Big Picture" Differences Involving Vaccines

- Administered infrequently during lifetime, hence lower volumes than maintenance treatment medicines
- Producers encounter greater difficulty identifying persons who will most likely benefit from therapy, resulting in less ability to capture consumer surplus through high prices – vaccines typically less profitable than branded pharmaceuticals, biologics
- Organized ideological and political opposition to the utilization of vaccines
- Relatively small dollar sales revenues (< $Lipitor)
- Development and distribution involves extensive private-public collaboration

Relatively Small U.S. Vaccine Sales Revenues, But Growing Very Rapidly since 2005

Year	Vaccines	Other Biologics	Pharmaceuticals	Total	Vaccines / Total (%)
2001	$2.2	$14.4	$160.1	$176.7	1.25%
2002	2.2	18.3	177.1	197.6	1.11
2003	2.7	22.5	196.4	221.6	1.22
2004	2.4	26.7	211.7	240.8	1.00
2005	2.8	31.9	219.4	254.1	1.10
2006	3.5	34.2	225.9	263.6	1.33
2007	6.1	35.4	233.9	275.4	2.21
AAGR	18.5%	16.2%	6.5%	7.7%	

Notes: Data provided by Murray Aitken, IMS Health. AAGR is average annual growth rate, 2001-2007; billions of current dollars

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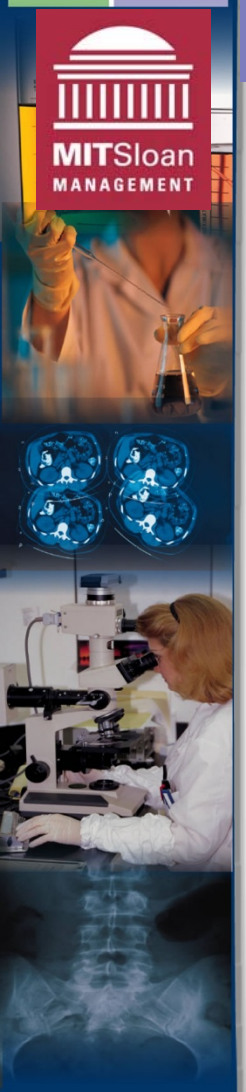
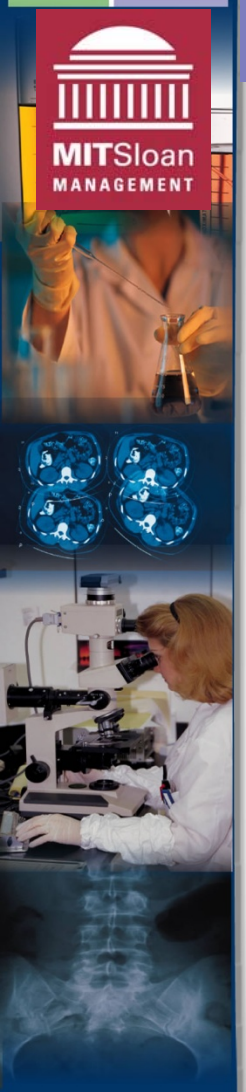
- Industry structure and concentration



Importance of Intellectual Property Protection to Vaccines

- In most cases, IP plays relatively minor role compared to that in other biologics and pharmaceuticals
- But exceptions do occur – manufacturing process rather than product patents, and patents covering adjuvants (additives that enhance potency and strengthen antibody response) are important assets
- Tamiflu and Relenza not vaccines, but used for treating flu symptoms, preventing cascade – calls again for suspending Roche's IP and implementing compulsory licensing to increase global supply – sales volatile as public interest in avian/swine flu swings wildly



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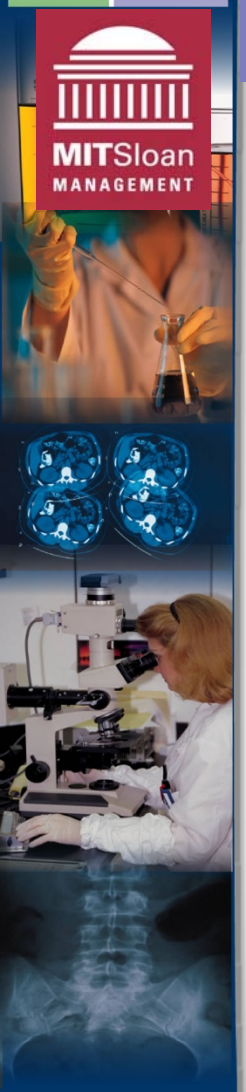

Differences: Pre-clinical and Clinical Development - I

- Big important difference – administered to very large numbers (millions) of healthy, happy kids
- Doing harm to healthy child more dreadful than harming health of already disease-stricken infant – safety requirements ***very rigid*** for vaccines – 140,000 kids in Phase III rotavirus vaccine trials
- Because prophylaxis is often intended to be long-lived, vaccine follow-up longer than for most biologics and pharmaceutics

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Differential Manufacturing, Scale-up and Cost Characteristics: I

- Scale-up decision for vaccines and biologics needs to be made relatively early in development process – already in Phase II before pivotal trials, unlike pharmaceuticals
- For new vaccine, takes 3-5 years to build facility, customized capital-intensive equipment, has no alternative use – sunk costs a greater risk than for pharma, but more like biologics
- For seasonal influenza vaccines, three target viral strains updated annually -- involves WHO/CDC/FDA and others
- Current chicken egg-based system is time-consuming and difficult to scale rapidly, leaving countries vulnerable to manufacturing problems and emergence of unanticipated avian/swine/other strains. Novartis is building mammalian cell-based plant in Hickory Hill, NC, more flexible and scalable, but not fully operational until 2012 at earliest.
- Meanwhile, search for “universal” vaccine intensifies

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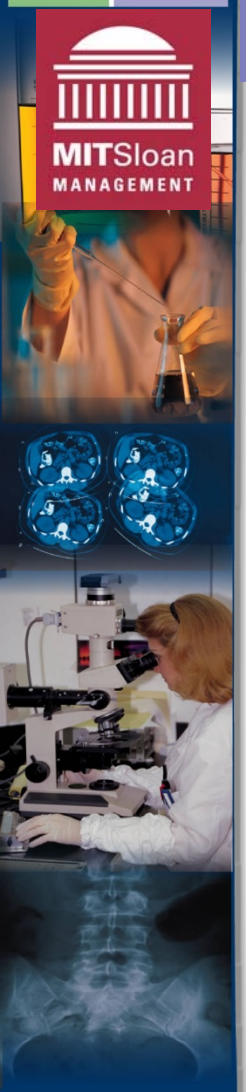
Coordination with Public Health Officials and Payers

- Early interactions with CDC/ACIP (Advisory Committee on Immunization Practices) to assure ultimate product fits into recommended vaccination schedules and guidelines
- Cost-effectiveness not legally required by CDC, but *de facto* absolutely necessary – reflects large sophisticated public sector purchasing role
- ACIP makes recommendation decisions only after the FDA approves the vaccine. If recommendation from ACIP is tepid (e.g., Lyme Rx) or withheld, market success unlikely (LymeRx withdrawn)
- ACIP recommendation for universal vaccination triggers Vaccines for Children Program entitlement funds to uninsured children -- automatic entitlement, not discretionary budgeted



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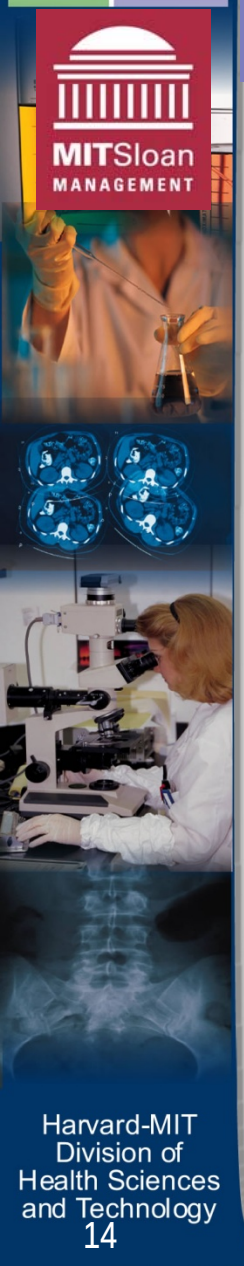

Differences in Distribution and Delivery Channels, and Payers: I

- Vaccine distribution typically shipped in single/multi-dose vials bulk to state collection depots; in considerably smaller volumes directly from manufacturer to private clinics and offices, who purchase from and bear inventory/cold chain equipment costs of storing vaccines; and to wholesalers who may repackage for physicians and clinics. This very different from pharmaceuticals, but similar to some biologics
- Return policies for spoiled/unused/expired product are important component of non-price competition
- McKesson Specialty awarded exclusive CDC Vaccines for Children distributor – becoming like specialty pharmacies?

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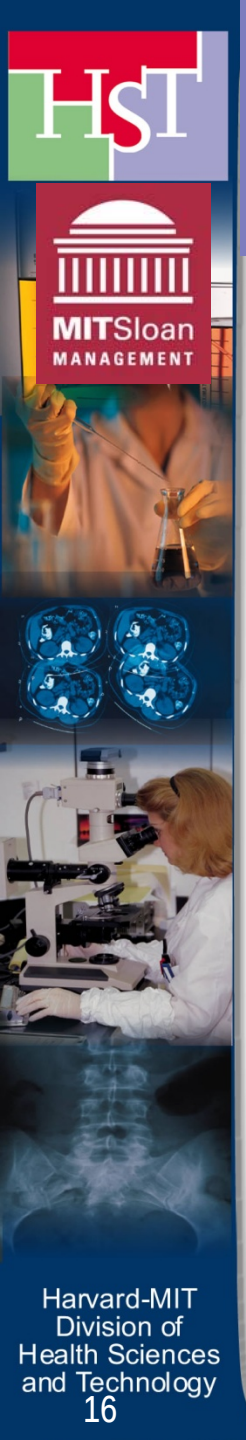

Differences: Product Liability Issues

- Mass vaccinations inevitably involve risk of adverse events – has increased with number of ACIP recommended vaccines
- Pertussis component of DTP combo vaccine associated with autism – liability costs responsible for 96% of 40-fold increase in 1980-87 prices of DTP (vs. DT) – resulted in no-fault National Vaccine Injury Compensation Program funded by $0.75 excise tax on each dose/disease – but can opt out. Adolescents/adults?
- Currently about 300 suits involving thimerosal preservative unsettled – today use of thimerosal almost fully phased out
- Recent VICP ruling on autism and measles vaccinations, with more to come soon…

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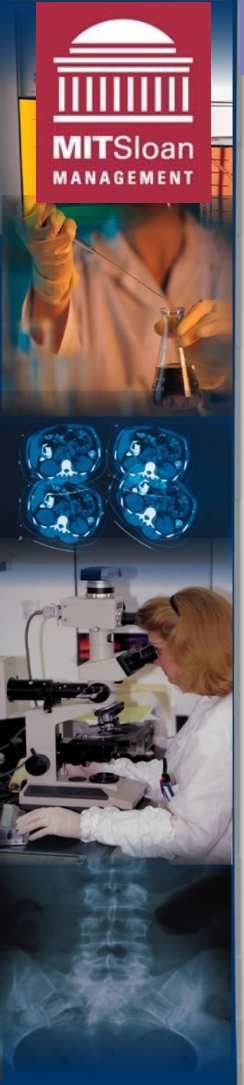
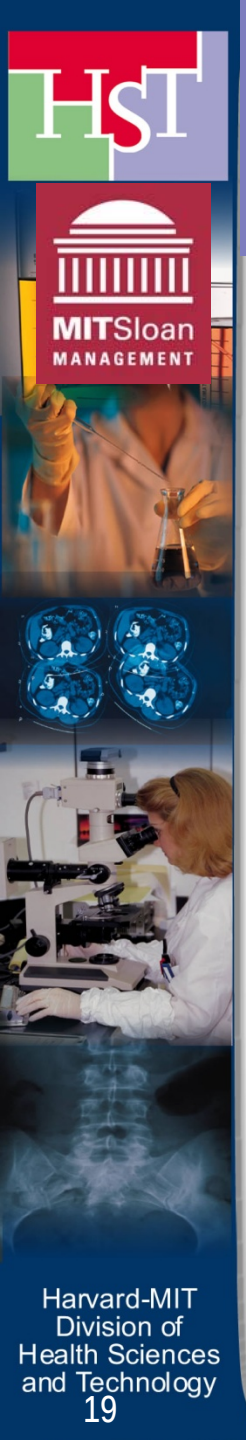


Differences in Pricing, Product Differentiation and Marketing: I

- Currently no generic vaccines in the developed world, unlike pharmaceuticals; many DTP combos, but little therapeutic competition among vaccines; related recent "follow-on" biologics controversy is ongoing
- Why no generic vaccines?
- Qualifying manufacturing facilities is costly and risky, given competition from next generation variant, especially if supported by ACIP recommendations
- Existence of scale economies implies lowest-cost manufacturer can capture entire market, especially with winner-take-all bidding – so price to keep competition out – "Bertrand" competition



Differences in Pricing, Product Differentiation and Marketing: II

- For old vaccines there are few manufacturers, very low prices – CDC price is 30-50% of that charged in the more decentralized private sector
- For newer patent-protected, sole source vaccines, there are higher prices (supported by cost-benefit studies), and smaller 15-20% discounts to public sector
- Examples: Prevnar ($71.04 for each of four doses), Varivax ($64.53 for each of two doses), and Gardasil ($105.58 for each of three doses) – all 2009 CDC prices

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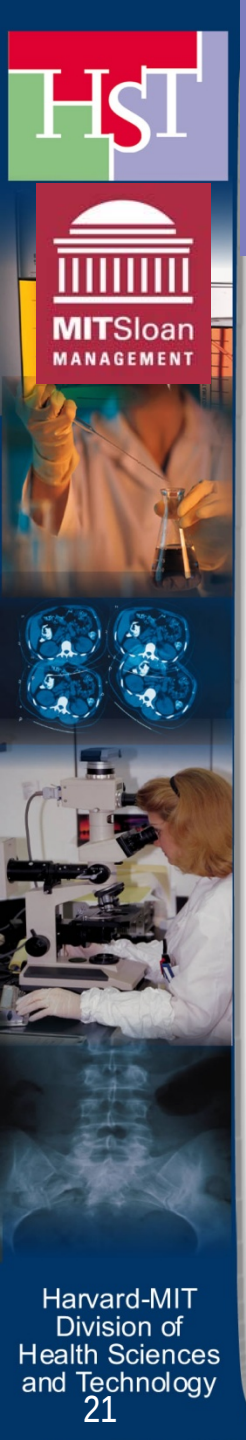

Differences in Post-Launch Surveillance

- FDA often requires post-launch study as condition for approval
- Similar to FDA's Adverse Events Reporting System (voluntary reporting by manufacturers), there's a VAERS – joint with CDC
- Claims data not as good for tracking vaccinations as for prescriptions filled – national population registry for pediatric vaccines efforts underway but incomplete – worse for adults. But CDC's Vaccine Safety Data Link contains claims for enrollees in seven major HMOs

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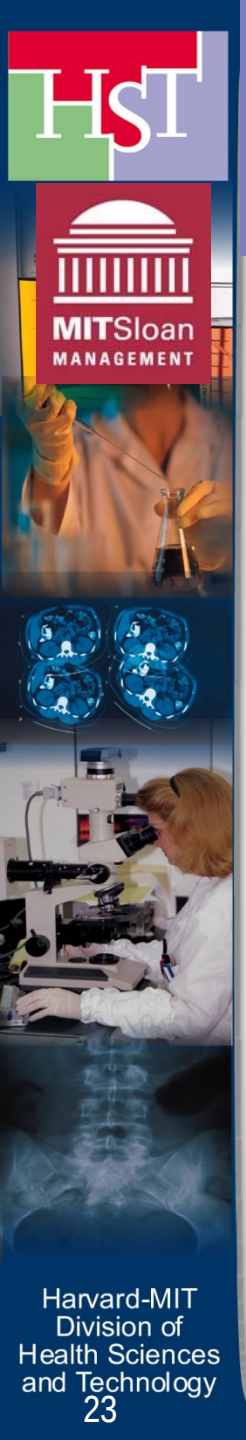
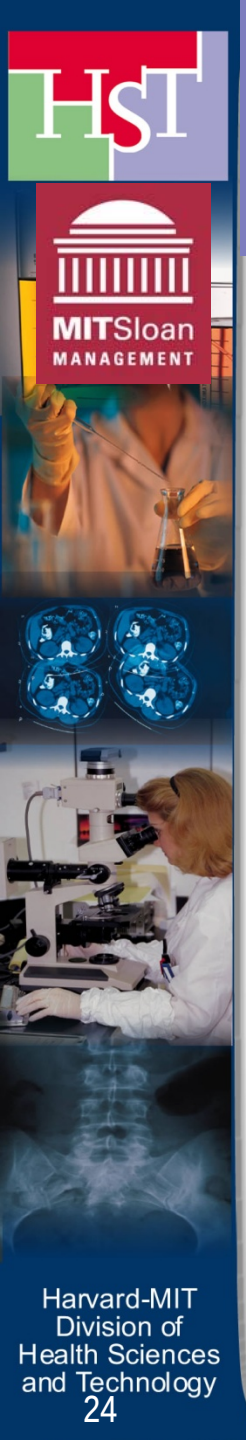


Industry Structure, Concentration and Shortages

- Combination of scale economies, regulatory policies, price bidding procedures, concentrated purchasing power, market acceptance of ACIP recommendations, and obsolescence from improved vaccine formulations has resulted in very few (1-2, except for influenza, 5) manufacturers of each vaccine
- Number of companies manufacturing vaccines in US was 26 in 1967, 17 in 1980, to 3 in 2004 (Sanofi-Pasteur, Merck and Wyeth) – Chiron, GSK ex-US, MedImmune part US, part UK
- Numerous sole suppliers vulnerable to supply and demand shocks – vaccines for 9 of 12 vaccine-preventable childhood diseases have experienced shortages since 2000 – followed in some cases by excess, unsold supplies (e.g., annual flu vaccines). Currently shortages exist for Varicella, Zoster, haemophilus influenzae type B, & monovalent versions of MMR

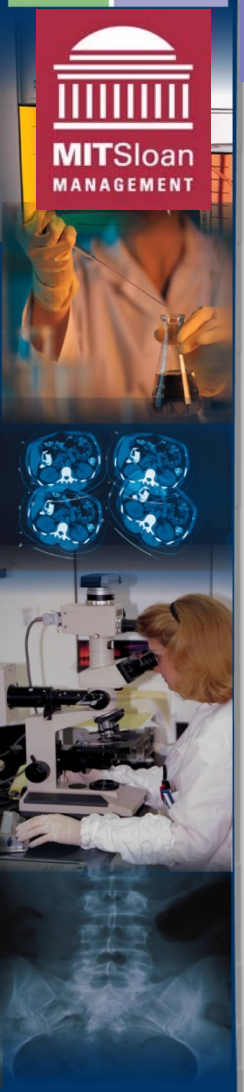


Case Studies

- Prevnar
- Seasonal influenza
- Varicella (chicken pox)
- Diptheria, Tetanus, and Pertussis

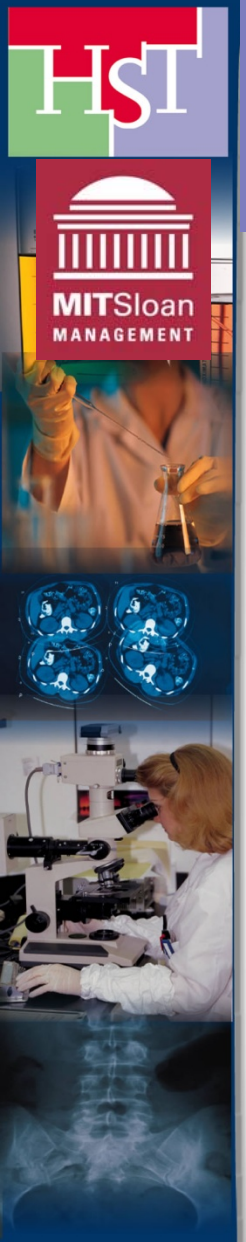
Prevnar Overview

- Launched in 2000 by Wyeth for immunization of infants and toddlers against pneumococcal diseases (pneumonia, bacterial meningitis, upper respiratory infections, etc.)
- First pneumococcal vaccine for infants (conjugate technology elicited stronger immune response in infants)



Prevnar: Clinical Trial/Post Marketing Surveillance

- Large scale Phase 3 trial enrolled 38,000 infants
- $38M clinical trial cost due to large number of enrollees as well as continuance of trial into Phase 4 post marketing surveillance
- Post marketing surveillance conducted by CDC found Prevnar has positive externalities
  - For every direct case of pneumoccocal disease prevented in children, two cases were indirectly prevented
  - Prevnar benefits spilling over into adult population

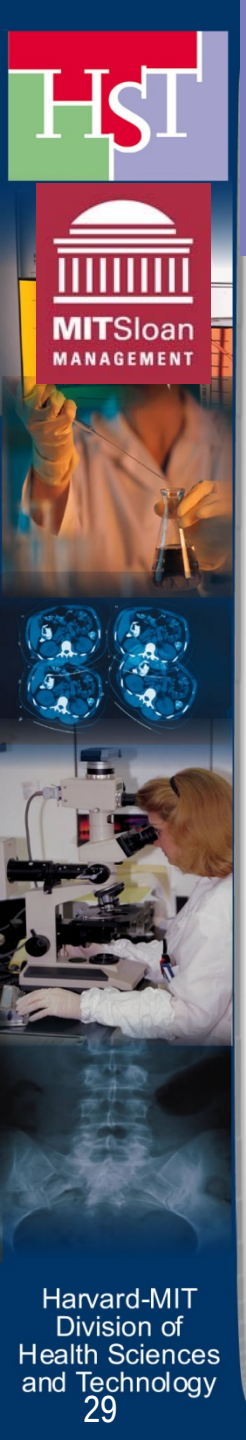


Prevnar: Manufacturing

- Experienced shortages soon after launch due to higher than anticipated demand
  - Unexpectedly, Wyeth became sole supplier of vaccine due to clinical development obstacles experienced by competitors
  - ACIP recommended Prevnar for all children ages 2 and younger as well as catch up vaccinations for children up to 5 years of age (large patient population)
  - Manufacturing process extremely complex (over $300M has been invested in Prevnar manufacturing facilities)

Pricing Prevnar: Paradigm Shift

- Wyeth's vaccine group under pressure to demonstrate value of vaccine franchise
- CDC released Prevnar cost effectiveness study with breakeven price at $46/dose
- Wyeth highlighted Prevnar's indirect benefit to society due to lower parent absenteeism from work
- Priced Prevnar at $58/dose
- By 2006, became 1st blockbuster vaccine, $2.7Bn in sales in 2008



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Seasonal Influenza Vaccine Manufacturers

Manufacturer	Vaccine	Launch Year	Administration	Recommended Age Group
Sanofi Pasteur	Fluzone	1970s	Injectable	6 mos+
Novartis	Fluvirin	1970s	Injectable	4+
GlaxoSmithKline	Fluarix	2005	Injectable	18+
GlaxoSmithKline	FluLaval	2006	Injectable	18+
CSL Biotherapies	Afluria	2008	Injectable	18+
MedImmune	FluMist	2003	Intranasal	2+

MedImmune's FluMist: Tepid Reaction

- Launched in 2003 with novel intranasal administration
- However, lackluster uptake of product by physicians
  - Initially, no physician reimbursement for intranasal administration
  - Inconvenient freezer storage requirement
  - Restricted to individuals age 5-49
- Second generation product launched in 2007
- Grew sales from $36M in 2006 to $104M in 2008

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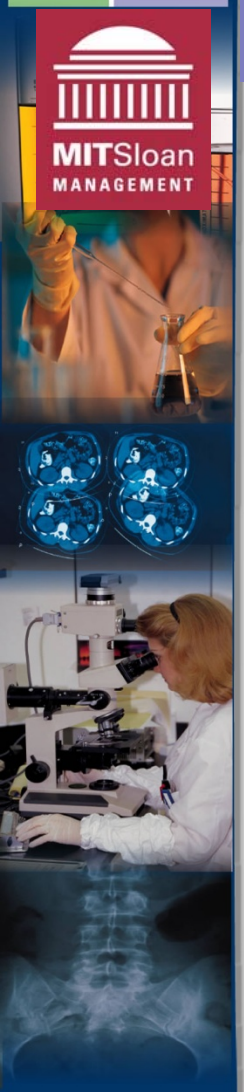
Seasonal Influenza Vaccine: Annual Production Timeline

- Jan-Mar: WHO & CDC predict & select 3 most common flu strains for upcoming flu season
- Jan-July: Viral strains are individually incubated and grown in chicken eggs
- July-Oct: Viral strains purified, inactivated, fragmented, combined, and tested
- Aug-Nov: Vaccine available to physicians



Seasonal Influenza Vaccine: Cell based production

Advantages

- Reliability of supply
- No contraindication for people allergic to eggs
- Perhaps enhanced immunogenic response
- Potentially greater yield

Disadvantages

- Annual updates will still be required
- Intense scale-up still unlikely

Seasonal Influenza Vaccine: Universal Vaccine

- Target multiple strains of flu eliminating need to update vaccine annually
- Development in very early stages
  - VaxInnate: Completed Phase 1 in 2008
  - Acambis: Completed Phase 1 in 2008
  - Dynavax: Expected to initiate Phase 1 in 2010
  - St. Louis University: Recently presented Phase 1 findings