Update on Vaccines in Dermatology

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DISCLOSURES

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- Consultant: GSK, Merck, Astellas, Novartis, Epiphany, Catalyst
- Pharmaceutical corporation stock: none
Prevention=Public Health + Vaccination

• Vaccination began with Jenner: cowpox (now vaccinia) to prevent smallpox: 1797 to 1977: first and only infectious disease eradicated
• Next targeted virus: polio, but goal to eradicate polio by 2005 (50th anniversary of 1st polio vaccine) not met
• Measles/mumps/rubella: now rare diseases in USA and Europe, but during 2014, 644 cases of measles were reported in the USA; most of these cases were imported.
Smallpox:

massive excretion of poxviruses.

Note lesions also on the tongue
Positive reaction at vaccine (vaccinia) inoculation site
Vaccines and Public Health

• Vaccines should be used in combination with public health measures:
• Safer sex; condoms; not sharing needles, cocaine straws, etc.
• Hand washing; respiratory precautions;
• Safer water and sewage
• Isolation, education, vector control, etc.
Vaccines against Bacterial Diseases

• Tetravalent meningococcal conjugate (MCV4) vaccine (and MPSV4)
• Tetanus toxoid, diphtheria toxoid and acellular pertussis (Tdap) vaccine
• Haemophilus influenzae b (Hib) vaccine
• Pneumococcal vaccine
• Typhoid vaccine
• Anthrax vaccine
• Cholera vaccine
• BCG (PPD vs. Quantiferon Gold)
Vaccines for Prevention of Fungal and Protozoan Diseases

- A Vaccine for Malaria.
- [White NJ.](https://doi.org/10.1056/NEJMoa1110148)
- It's been a long time coming, and indeed we are still not there yet, but it is becoming increasingly clear that we really do have the first effective vaccine against a parasitic disease in humans. If there are no unforeseen disasters, the RTS,S/AS01 Plasmodium falciparum malaria vaccine should become available in just over 3 years. The World Health Organization (WHO) has already taken the unusual step of indicating that it could recommend this first malaria vaccine for use in some African countries as early as 2015, depending on the full phase 3 trial results that will become available in 2014. . . .
Vaccine Safety

• FDA approved vaccines are at least a million fold safer than the viruses they are designed to prevent
• Does MMR vaccine cause autism?
• No, according to FDA, CDC, IOM, computerized health networks of several European countries, but------
• Yes, according to the National Autism Assn. (a lay, advocacy group)
MMR/Autism

• MMR is given at one year of age, but autism is usually not easily diagnosed before 2 years of age;
• To the lay public, one event preceding another event means “cause and effect”
• Antivaccination web sites express a range of concerns related to vaccines safety and varying levels of distrust in medicine
There is More to Fear than Just the Viruses

• Deer: How the case against the MMR vaccine was fixed. BMJ 2011 Jan 5; 342:c5347.

• Godlee, Smith, Marcovitch: Wakefield’s article linking MMR vaccine and autism was fraudulent. BMJ 2011 Jan 5; 342: c7452.
MMR Decreases Risk of Hospital Admissions for Nontargeted Infections

• A study of 495,987 children in Denmark showed that receiving MMR not only decreased hospital admissions for these infections, but also lower the rate of admission for any infections

• JAMA 311: 826-835; 2014.
Routes of Vaccination

• Most vaccines are given via injection, but oral polio vaccine, oral rotavirus vaccines and intranasal influenza vaccine have been available for years

• New routes of vaccination: topical patches (e.g. Dupont et al: E. coli vaccine, *Lancet* 372: 2019-2025; 2008); intravaginal, etc.
Vaccines and Biologic Therapy for Psoriasis

• It is best to vaccinate before starting biologics, but

• It may be best to wait one half-life pre/post vaccination with a killed, recombinant or subunit vaccine; and

• Wait two half-lives pre/post live attenuated vaccines
Biologics/Shingles & PHN

- Possible association of lower rate of postherpetic neuralgia in patients on anti-tumor necrosis factor-α.
- Javed S, Kamili QU, Mendoza N, Tyring SK.
- Source
  University of Texas Medical School at Houston, Houston, Texas, USA. sabajaved23@gmail.com
- Abstract
  Recently, a study of patients with rheumatoid arthritis who developed herpes zoster while taking a tumor necrosis factor (TNF)-α inhibitor reported a decreased incidence of postherpetic neuralgia. The objective of this study was to investigate whether patients on TNF-α inhibitors who developed herpes zoster have a lower incidence of subsequent development of postherpetic neuralgia. A retrospective review of herpes zoster patients on TNF-α inhibitors (infliximab, etanercept, or adalimumab) was conducted in 12 dermatology clinics. Medical records of such patients were reviewed thoroughly to confirm herpes zoster and TNF-α inhibitors and any subsequent development of postherpetic neuralgia (pain score ≥ 3 out of 10 after 90 days of shingles onset) was noted. A total of 206 cases were reviewed, of which only 2 cases (<1%) developed postherpetic neuralgia, a considerably lower incidence rate than noted in the literature. Increasing age is a known risk factor in the development of postherpetic neuralgia. However, of the 58 (28.1%) cases ≥ 70 years of age, only 1 patient (1.7%) developed neuralgia compared to approximately 50% of patients who develop postherpetic neuralgia in this age group as reported in the literature. Treatment with TNF-α inhibitors may be associated with a lower incidence of postherpetic neuralgia but further prospective large-scale studies are needed to confirm this data.
Influenza vaccines

• Human influenza vaccines are grown in chicken eggs: very inefficient; better technologies needed
• Consequences of avian influenza on human influenza vaccine production?
• In 2016 the CDC recommended the recombinant influenza vaccine (RIV) which uses genetically engineered insect virus containing genes encoding hemagglutinin
Influenza 2017

- Most of the thousands of influenza deaths in the 2016-17 season were elderly or immunocompromised, but 104 pediatric deaths
- Influenza A (H3N2) is most common now
- Most influenza vaccines protect against H1N1, H3N2 and one influenza B strain, but nasal spray (quadrivalent) vaccine also protects against a second B strain
- Current vaccines have minimal protection (23%) in some individuals, but it is better to be vaccinated than not
Influenza 2017

• At first symptom/sign of influenza or even exposure in high risk individuals, start
• Oseltamivir (Tamiflu) (oral) or
• Zanamivir (Relenza) (inhaled) or
• Peramivir (Rapivab) (intravenous)
Varicella/Varicella Zoster

- Attenuated vaccine, Varivax, FDA approved in 1995, is safe and effective to prevent chickenpox (two injections if over 12 months)
- Varivax was FDA approved 9/6/05 to be given with MMR as “Proquad”
- Immunity appears to last 25+ years
- When given to adults who had chickenpox in past, it decreased the incidence of shingles by 51% and the incidence of PHN by 66% (N Engl J Med 352: 2271-2284; 2005). Zostavax, the 14-fold concentrated version of Varivax, was approved in May 2006 for prevention of herpes zoster in persons >60 years (without history of shingles)
Disposition of Study Subjects

Enrolled 38,546

Zoster vaccine 19,270
- Terminated before end of study: 793 (4.1%) Died
  57 (0.3%) Withdrew
  61 (0.3%) Lost to follow-up
- Completed study: 18,359 (95.3%)

Placebo 19,276
- Terminated before end of study: 792 (4.1%) Died
  75 (0.4%) Withdrew
  52 (0.2%) Lost to follow-up
- Completed study: 18,357 (95.2%)

Vaccine Efficacy for Incidence of Herpes Zoster

Efficacy (95% CI)

- All: 51.3% (44.2%–57.6%) (p<.001)
- 60-69: 63.9% (ND)
- ≥70: 37.6% (ND)

Incidence of herpes zoster

Vaccine Placebo

Age (years)

ND=not determined.

ZOSTAVAX® (Zoster Vaccine Live) Efficacy and Safety Trial (ZEST) in Subjects 50–59 Years of Age

LOWER INCIDENCE OF ZOSTER

Efficacy of ZOSTAVAX on Zoster Incidence Compared with Placebo

Results from ZESTa show that ZOSTAVAX significantly reduced the risk of zoster.

Vaccination with ZOSTAVAX does not result in protection of all vaccine recipients.

Study Design for ZEST: In the ZOSTAVAX Efficacy and Safety Trial, efficacy was evaluated in a placebo-controlled, double-blind study of ZOSTAVAX. 22,439 subjects 50 to 59 years of age were randomized to receive a single dose of either ZOSTAVAX (n=11,211) or placebo (n=11,228) and were monitored for the occurrence of shingles for a median of 1.3 years postvaccination (range 0 to 2 years).
Vaccine Efficacy for Incidence of PHN

Efficacy (95% CI)
- 66.5% (47.5%-79.2%)
- 65.7% (20.4%-86.7%)
- 66.8% (43.3%-81.3%)

Incidence of PHN

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>60-69</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>≥70</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Safety of Zostavax

- Recipients of Zostavax had higher rates of local reactions (erythema, swelling, etc.) than did recipients of placebo
- Recipients of Zostavax and placebo did not differ in systemic adverse events
Questions regarding the Shingles Vaccine

- Use in persons under 50 years?
- Use in persons with history of shingles?
- Use in persons without a history of chickenpox?
- Use as therapy for shingles or PHN?
- Use in immunocompromised patients?
- Implications for therapeutic HSV vaccine?
Therapeutic HSV2 Vaccination

- Genocea: GEN-003 includes the antigens ICP4 and gD2 along with Matrix-M2TM adjuvant;
- Vical: two vaccine candidates (one encoding glycoprotein D alone and the other in combination with UL46);
- Agenus: HerpV is comprised of a mixture of peptides for HSV-2 antigens as well as the company’s QS-21 Stimulon adjuvant.
Therapeutic HSV Vaccines

• In phase I/II clinic trials, all three vaccines were shown to be safe and effective for reducing clinical outbreaks (i.e. lesions) and for reducing asymptomatic viral shedding.
Future of Zoster Vaccination

• “Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults”.
  15,411 participants >50 years evaluated
  Efficacy was 97% in all age groups at 3.2 yr
  Safety: local reactions (similar to Zostavax)
Will the Shingles Vaccine Decrease the Prevalence of Herpes Zoster?

- 51% efficacy; duration of benefit unknown
- FDA approval for persons > 50 years
- Insurance coverage?
- Low compliance with recommended vaccines
- Contraindicated in immunocompromised (IC) patients
- Elderly and IC populations increasing
- Decreased wild type VZV: less immune boosting (?): not according to http://jama.md/1cwa5MA which showed a 39% increase in zoster/20 years
Human Papillomavirus (HPV) Vaccines

HPV-6/11/16/18 VLPs

- L1 capsid proteins made in insect cells using yeast/insect cell system
- Formulated with alum/MPL
- 3-doses: months 0, 1/2, 6
- Elicits neutralizing antibody to HPV- Th1 dominant CMI
What’s New in Prevention: 9-valent HPV vaccine

• Potentially can prevent >90% of cervical cancers (and other ano-genital/oral HPV-related cancers)
• Three doses (IM): months 0, 2 and 6
Human Papillomavirus (HPV) Vaccines

HPV6/11/16/18 (Gardasil)/31/33/45/52/58 VLPs = Gardasil 9

- L1 capsid proteins made using yeast/insect cell system
- Formulated with AAHS (amorphous aluminum hydroxyphosphate sulfate) adjuvant
- Elicits neutralizing antibody to HPV- Th1 dominant CMI
Efficacy Against HPV 6/11/16/18–Disease in Per-Protocol Population

95% confidence interval: 94%–100%.
CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia;
VaIN = vaginal intraepithelial neoplasia; FUTURE = Females United To Unilaterally Reduce Endo/Ectocervical Disease.

GARDASIL
Placebo

100% efficacy
100% efficacy

n=2,241
n=2,258
n=2,261
n=2,279

0
0
Efficacy Against HPV 6/11/16/18–Disease In Unrestricted Susceptible Population

![Graph showing efficacy against HPV 6/11/16/18-related disease in CIN or AIS and VIN/VaIN/Genital Warts.

95% confidence interval: 92%–100% for CIN and AIS and 87%–99% for VIN/VaIN/genital warts. CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal Intraepithelial neoplasia; FUTURE = Females United To Unilaterally Reduce Endo/Ectocervical Disease.

## HPV Vaccine Safety

### Summary of Safety

<table>
<thead>
<tr>
<th></th>
<th><strong>FUTURE I</strong></th>
<th></th>
<th><strong>FUTURE II</strong></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>GARDA SIL</strong></td>
<td>Placebo</td>
<td><strong>GARDA SIL</strong></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>( n=2,673 )</td>
<td>( n=2,672 )</td>
<td>( n=6,019 )</td>
<td>( n=6,031 )</td>
</tr>
<tr>
<td>Injection-site AE</td>
<td>86.8</td>
<td>77.4</td>
<td>84.4</td>
<td>77.9</td>
</tr>
<tr>
<td>– Pain</td>
<td>85.3</td>
<td>75.4</td>
<td>83.0</td>
<td>75.8</td>
</tr>
<tr>
<td>Systemic AE</td>
<td>65.3</td>
<td>63.7</td>
<td>61.4</td>
<td>60.0</td>
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<tr>
<td>Serious AE</td>
<td>1.8</td>
<td>1.7</td>
<td>0.7</td>
<td>0.9</td>
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<tr>
<td>Serious vaccine-related AE</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
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<tr>
<td>Discontinuation due to serious AE</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Discontinuation due to serious vaccine-related</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
Measles/ rubeola
Measles

• 644 cases in USA in 2014; the most cases in the 21st century
• June 6, 2015 (from CDC): > 176 cases from visiting Disneyland, CA
• Reason: non-compliance with recommended vaccinations
New Vaccines

- HSV vaccine safe and effective
- First HIV vaccine was not effective, but many new candidate vaccines
- Need for vaccine against hepatitis C
- Need for better production methods for influenza vaccines
- Other viral diseases: Zika, Chikungunya, Ebola, West Nile virus, new respiratory infections, e.g. SARS & MERS
Conclusions

Over 40 antiviral drugs and >25 viral & bacterial vaccines are available. They should be used in combination with good public health measures.

Vaccines needed for HIV, HSV, hepatitis C, influenza, Zika, Chikungunya, Ebola, SARS/MERS, West Nile, as well as for many bacterial, fungal and protozoan diseases.
QUESTIONS?