Time to make the point of VZV generalized vaccination

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Conflicts of interest

Paolo Bonanni received grants for epidemiological and HTA research from different vaccine companies (GSK, MSD, Sanofi Pasteur, Pfizer, Seqirus) and fees for taking part to advisory boards on different vaccines from the same companies.

Acknowledgment

Some of the presented slides were prepared jointly by Hanna Nohynek and myself for the workshop ‘Varicella: Looking for a valuable approach’, Brighton, UK, May 2016.
The issue
Varicella Zoster

- One virus
- Two distinct diseases (Varicella and Herpes zoster)
- Scarce consideration of disease burden in several countries (Varicella)
- Disease-specific vaccines

- A comprehensive approach to prevention needed
Varicella: burden of disease in Europe

592,681 varicella cases reported in EU
(18 countries) with incidence up to 481/100 000 (2010)¹

- Usually self-limiting, varicella can lead to potential serious complications in about 2-6% of cases attending a general practice ²

- Incidence of hospitalisation ranged from 12.9 to 28 per 100,000 children < 16 years of age with average duration of hospital stay ranging from 3-8 days ²

- Most complications & hospitalisation occur in children who were healthy ²

- Case Fatality Rate 1/100 000 in children 1-14 years vs. 25/100 000 in adults ⁴,⁵

² P Bonanni, Varicella vaccination in Europe-taking the practical approach BMC Medicine, 2009
³ http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-prevention-vaccinale/Varicelle/Qu-est-ce-que-la-varicelle accessed on 7-03-2014
⁴ Meyer, JID, 2000 ; ⁵ CDC, Pink Book, Varicella chapter, 2013
Varicella high incidence and seroprevalence

Annual incidence (cases per 100,000 population): 4,400–18,600 for children aged 0–4 years
Without vaccination, >90% of children are seropositive by adolescence in temperate areas, but with rather important differences among countries reflecting different $R_0$ values.

Varicella: only a ‘mild disease’?

**Viral**

- Congenital infection
- Pulmonary (1/400)
- Hemorrhagic
- Neurological (acute cellular ataxia – 1/4,000 cases, encephalitis – 1/100,000 cases, Reye’s Syndrome)

**Varicella complications**

**Bacterial**

- Bacterial superinfection of lesions
- Pneumonia (pneumonitis, varicella pneumonia)
- Bacteremia, sepsis

(1/3,000 cases)

Complications are most common in:

- older age groups,
- pregnant women (including congenital varicella syndrome and neonatal varicella)
- Immunocompromised patients

Varicella is responsible for a substantial burden of hospitalisations, with variations among countries

Varicella usually not notifiable

Real burden of disease and clinical impact is unknown in many countries in EU and outside EU

- Case-based data at national level from mandatory reports
- Aggregated data at national level from mandatory reports
- Laboratory-based mandatory reports
- Only sentinel surveillance
- No surveillance
- No information

Varicella vaccine: efficacy
Varicella-containing vaccines: efficacy in clinical studies

<table>
<thead>
<tr>
<th>Follow-up, years</th>
<th>One dose of VARIVAX</th>
<th>Two doses of VARIVAX</th>
<th>One dose of Varilrix*</th>
<th>Two doses of Priorix-Tetra*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>94.4 (92.2, 95.7)³</td>
<td>98.3 (97.3, 99.0)³</td>
<td>65.4 (57.2, 72.1)¹</td>
<td>94.9 (92.4, 96.6)¹</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>69.5 (61.5, 78.8)²</td>
<td>95.3 (93.1, 96.8)²</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>100³</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>90.7 (85.9, 93.9)¹</td>
<td>99.5 (97.5, 99.9)¹</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>91.8 (85.6, 95.2)²</td>
<td>98.4 (95.5, 99.4)²</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are %, (95% CI)

*The posology within the Summary of Product Characteristics for Varilrix™ and Priorix-Tetra™ is two injections.³,⁴

Universal varicella vaccination: effectiveness and impact
Vaccine effectiveness of one- and two-dose strategies

WHO recommends that direct and indirect costs should be considered when assessing the cost:benefit ratio of a given vaccination schedule\(^{12}\)

Reference: country; coverage; brand; study year(s)
1. Germany; 25%; GSK/Merck; 2008–10
2. USA; NR; Merck; 2006–10
3. China; low*; GSK/other; 2002–05
4. Taiwan; 71%; NR; 2007
5. USA; 100%; NR; 2011
6. Germany; 62%; GSK/Merck; 2008–09
7. Italy; 54%; NR; 2009
8. Italy; 21–82%; GSK/Merck; 2011
9. China; NR; GSK/Other; 2010–11
10. USA; 100%; Merck; 1995–2009
11. Taiwan; NR; GSK/Merck; 2000–07

\(^*\)Low coverage rate was not defined in the paper.

Impact of two-dose URV on overall rate of varicella in USA (1996–2008)

Incidence of breakthrough varicella in the USA over 14 years

- Decrease by 9 to 10 times the average incidence of varicella over the 14-year compared to pre-vaccination era.
- No waning noted

Varicella vaccination impact on mortality in USA

Annual varicella-related deaths in the USA, national vital statistics system data, 1990–2011

Varicella vaccination impact in Italy

**Varicella incidence in Puglia, Italy (long schedule)**

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (x1,000)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- **1-dose introduced (aged 15 months)**
- **2-dose introduced (aged 5–6 or 11–12)**

**Varicella incidence in 8 Italian regions**

Varicella vaccination impact on hospitalisations in Italy

A two-dose schedule was used in 8 Italian regions\textsuperscript{1}

In Italian regions, the reduction in hospitalisation rate\textsuperscript{1,2} led to an associated decrease in the costs of hospitalisation\textsuperscript{1}

Preparing to introduce the varicella vaccine into the Italian immunisation programme: varicella-related hospitalisations in Tuscany, 2004–2012

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Correspondence: Paolo Bonanni (paolo.bonanni@unifi.it)

Figure 4

Total cost of hospitalisation for varicella diseases, by age group, Tuscany, Italy, pre-vaccination (2004–2007) and vaccination periods (2009–2012)

Table

Hospitalisations for varicella diseases, by age, and hospitalisation risk ratios with 95% CI, Tuscany, Italy, pre-vaccination (2004–2007) and vaccination periods (2009–2012)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pre-vaccination period 2004–2007</th>
<th></th>
<th>Vaccination period 2009–2012</th>
<th></th>
<th>HRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospitals</td>
<td>Average rate per 100,000</td>
<td>Hospitals</td>
<td>Average rate per 100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>73</td>
<td>59.8</td>
<td>42</td>
<td>37.7</td>
<td>0.55</td>
<td>0.38–0.80</td>
</tr>
<tr>
<td>1–4 years</td>
<td>109</td>
<td>29.5</td>
<td>99</td>
<td>18.0</td>
<td>0.48</td>
<td>0.38–0.64</td>
</tr>
<tr>
<td>5–14 years</td>
<td>105</td>
<td>9.2</td>
<td>55</td>
<td>4.5</td>
<td>0.48</td>
<td>0.35–0.67</td>
</tr>
<tr>
<td>15–24 years</td>
<td>32</td>
<td>2.6</td>
<td>21</td>
<td>1.7</td>
<td>0.64</td>
<td>0.52–0.79</td>
</tr>
<tr>
<td>25–49 years</td>
<td>141</td>
<td>2.7</td>
<td>67</td>
<td>1.3</td>
<td>0.47</td>
<td>0.35–0.69</td>
</tr>
<tr>
<td>50–64 years</td>
<td>23</td>
<td>0.8</td>
<td>16</td>
<td>0.5</td>
<td>0.67</td>
<td>0.52–0.83</td>
</tr>
<tr>
<td>64 years</td>
<td>21</td>
<td>0.6</td>
<td>25</td>
<td>0.7</td>
<td>1.34</td>
<td>0.64–2.46</td>
</tr>
<tr>
<td>Overall</td>
<td>586</td>
<td>4.1</td>
<td>325</td>
<td>2.2</td>
<td>0.54</td>
<td>0.43–0.62</td>
</tr>
</tbody>
</table>

CI: confidence interval; HRR: hospitalisation risk ratio.
Varicella vaccine: post-marketing safety
Varicella Virus Vaccine Live: A 22-Year Review of Postmarketing Safety Data
Meredith Woodward, Ann Marko, Susan Galea, Barry Eagel, and Walter Straus

Background. Varicella, a contagious infectious disease caused by varicella zoster virus (VZV), can result in hospitalization and, occasionally, death. Varicella virus vaccine live (VVVL [VARIVAX]) was introduced in the United States in 1995.

Methods. This comprehensive review of the VVVL safety profile is based on 22 years of postmarketing adverse event (AE) data received through spontaneous and noninterventional study reports submitted by health care providers and on a review of the published literature (cumulatively from March 17, 1995, through March 16, 2017, during which period >212 million doses were distributed globally).

Results. The VVVL safety profile was consistent with previous publications, with common AEs including varicella, rash, and pyrexia. AE reports have decreased over time, from ~500 per million doses in 1995 to ~40 per million doses in 2016; serious AEs comprise 0.8 reports per million doses. Secondary transmission was rare (8 confirmed cases); polymerase chain reaction analysis indicated that 38 of the 66 reported potential secondary transmission cases of varicella were attributable to wild-type VZV. The prevalence of major birth defects in the Pregnancy Registry was similar to that in the general US population. In total, 86 cases of death were reported after vaccination with VVVL; immunocompromised individuals appeared to be most at risk for a fatal varicella- or herpes zoster–related outcome.

Conclusions. This comprehensive 22-year review confirms the overall safety profile for VVVL, with no new safety concerns identified. Since VVVL’s introduction in 1995, notable declines in varicella cases and in varicella-related deaths have occurred compared with the prevaccination period.

Universal varicella vaccination: is it economically justified?
Universal Varicella Vaccination: Cost-effectiveness

Models ignoring the potential impact on HZ

- **Payer perspective** - childhood URV usually cost-effective or cost-saving
- **Societal perspective** - childhood URV was cost-saving
- Vaccination of adolescents was cost-effective or cost-saving
- Unclear whether adolescent or childhood vaccination is more cost-effective

Models including the potential impact on HZ

- Doubtful that childhood URV is cost-effective, at least for several decades

Effect of model methodology: static vs dynamic

<table>
<thead>
<tr>
<th>Static</th>
<th>Dynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Force of infection is constant over time</td>
<td>Force of infection depends on no. susceptible, infectious, and recovered individuals</td>
</tr>
<tr>
<td>Sufficient for models of HZ vaccination</td>
<td>Should be used for models of varicella URV</td>
</tr>
<tr>
<td>Force of HZ infection is constant by nature</td>
<td>Include herd immunity effects</td>
</tr>
<tr>
<td></td>
<td>Include impact on HZ incidence</td>
</tr>
</tbody>
</table>

HZ, herpes zoster; URV, universal routine vaccination.
Importance of vaccine-preventable disease incidence and severity on decision to introduce a vaccine

Case fatality rates and pre-vaccine prevalence of vaccine-preventable diseases in the USA

To be justified in terms of costs, added complexity, & efficacy

Recently recommended and future candidate vaccines

Universal varicella vaccination: how many doses?

What are the most important factors impacting varicella prevention?
Primary Versus Secondary Failure After Varicella Vaccination: Implications for Interval Between 2 Doses

Pauolo Bonannini, MD,* Anne Gershon, MD,† Michael Gershon, MD,‡ Andrea Kulcsár, MD,§ Vassiliki Papavangelou, MD, PhD,¶ Bernard Rentier, DSc, PhD,‖ Catherine Sadzot-Delvaux, PhD,¶‡ Vytanas Usonis, MD,*** Timo Vesikari, MD, PhD,†† Catherine Well-Olivier, MD,‡‡ Peter de Winter, PhD, §§ and Peter Wutzler, MD, §§§

The Pediatric Infectious Disease Journal • Volume 32, Number 7, July 2013

Background: Two-dose varicella vaccination is recommended for optimal control of varicella in populations with high (>90%) 1-dose coverage. Optimal timing of the second dose may depend on whether breakthrough varicella results from primary vaccine failure (no protective immunity after vaccination) or secondary vaccine failure (waning protective immunity).

Methods: Published literature (1995 to 2012) on vaccine failure after varicella vaccination cited in PubMed and other online sources was reviewed.

Results: Nineteen publications detailed 21 varicella outbreaks with breakthrough varicella rates ranging from 0% to 42%; the publications showed no consistent trend between breakthrough varicella rate and time since vaccination.

Conclusions: Literature to date indicates a relatively high rate of primary vaccine failure and limited evidence of secondary vaccine failure among 1-dose varicella vaccine recipients, suggesting that a short interval between 2 doses might be preferable in countries considering implementation of universal varicella vaccination to reduce breakthrough varicella. However, any potential disruption to well-established vaccination schedules should be considered.
Background: Varicella is a highly infectious disease with a significant public health and economic burden, which can be prevented with childhood routine varicella vaccination. Vaccination strategies differ by country. Some factors are known to play an important role (number of doses, coverage, dosing interval, efficacy and catch-up programmes), however, their relative impact on the reduction of varicella in the population remains unclear. This paper aims to help policy makers prioritise the critical factors to achieve the most successful vaccination programme with the available budget.

Methods: Scenarios assessed the impact of different vaccination strategies on reduction of varicella disease in the population. A dynamic transmission model was used and adapted to fit Italian demographics and population mixing patterns. Inputs included coverage, number of doses, dosing intervals, first-dose efficacy and availability of catch-up programmes, based on strategies currently used or likely to be used in different countries. The time horizon was 30 years.

Results: Both one- and two-dose routine varicella vaccination strategies prevented a comparable number of varicella cases with complications, but two-doses provided broader protection due to prevention of a higher number of milder varicella cases. A catch-up programme in susceptible adolescents aged 10–14 years old reduced varicella cases by 27–43 % in older children, which are often more severe than in younger children. Coverage, for all strategies, sustained at high levels achieved the largest reduction in varicella. In general, a 20 % increase in coverage resulted in a further 27–31 % reduction in varicella cases. When high coverage is reached, the impact of dosing interval and first-dose vaccine efficacy had a relatively lower impact on disease prevention in the population. Compared to the long (11 years) dosing interval, the short (5 months) and medium (5 years) interval schedules reduced varicella cases by a further 5-13 % and 2-5 %, respectively. Similarly, a 10 % increase in first-dose efficacy (from 65 to 75 % efficacy) prevented 2–5 % more varicella cases, suggesting it is the least influential factor when considering routine varicella vaccination.

Conclusions: Vaccination strategies can be implemented differently in each country depending on their needs, infrastructure and healthcare budget. However, ensuring high coverage remains the critical success factor for significant prevention of varicella when introducing varicella vaccination in the national immunisation programme.
Current situation of universal varicella vaccination and hurdles to its extension
Varicella vaccine recommendations worldwide

Implementing Universal Varicella Vaccination in Europe

The Path Forward

Vana Spoulou, MD,* Sophie Alain, MD† Giovanni Gabetti, MD‡ Carlo Giapponio, MD.§ Johannes Lisse, MD¶ Federico Martinom-Torres, MD‖ and Timo Vesikari, MD**

*The Pediatric Infectious Disease Journal • Volume 38, Number 2, February 2019

Barrier 1: Perceived Low Disease Burden and Low Public Health Priority

Barrier 2: Safety of MMRV After the First Dose

Barrier 3: Potential Epidemiologic Impact of Routine Childhood Varicella Immunization Programs on Varicella and HZ

Barrier 4: Cost-effectiveness and Funding Availability

<table>
<thead>
<tr>
<th>Country</th>
<th>UVV Recommendation Date</th>
<th>Implementation/Coverage</th>
<th>Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>2010</td>
<td>National but not implemented (no public funding)</td>
<td>D1 and D2 MMRV between 11 and 23 m (4-wk interval)</td>
</tr>
<tr>
<td>Finland</td>
<td>2017</td>
<td>National</td>
<td>D1 MMR+V, 12 m; D2 MMRV, 6 yr</td>
</tr>
<tr>
<td>Germany†</td>
<td>2004</td>
<td>National</td>
<td>D1 MMR+V, 11–14 m; D2 MMRV, 15–23 m</td>
</tr>
<tr>
<td>Greece†</td>
<td>2006</td>
<td>National</td>
<td>D1 MMR+V, 12–15 m; D2 MMRV, 4–6 yr</td>
</tr>
<tr>
<td>Italy†</td>
<td>First regional recommendation (Sicily) in 2002</td>
<td>National</td>
<td>D1 MMR+V, 13/15 m; D2 MMRV, 5–6 yr</td>
</tr>
<tr>
<td>Latvia*</td>
<td>2005</td>
<td>National</td>
<td>D1, 12–18 m</td>
</tr>
<tr>
<td>Luxembourg†</td>
<td>2009</td>
<td>National</td>
<td>D1 MMRV, 12 m; D2 MMRV, 15–23 m</td>
</tr>
<tr>
<td>Spain†</td>
<td>First regional recommendation (Navarra) in 2006 and then (National) in 2016</td>
<td>National</td>
<td>Navarra: D1 MMR+V, 15 m; D2 MMR+V, 3 yr; National: D1 MMR+V, 15 m; D2 MMRV, 2–4 yr</td>
</tr>
<tr>
<td>Cyprus</td>
<td>2010</td>
<td>National</td>
<td>D1, 13–18 m; D2, 4–6 yr</td>
</tr>
</tbody>
</table>

*All countries recommend a 2-dose regimen except Latvia, which recommends a 1-dose regimen.
†UVV is publicly funded.
D1 indicates dose 1; D2, dose 2; MMR+V, measles, mumps and rubella combination vaccine + varicella vaccine given separately.
Risk of febrile seizures after the first dose of MMRV combined vaccines

• Occurrence within 5-12 days/ 7-10 days days after the first dose of MMRV combined vaccines (ProQuad and Priorix Tetra) \(^1,2,3,4\)

• Risk:
  – one additional febrile seizure for every 2300 to 2600-2700 vaccinations compared to MMR+V vaccinations administered separately.\(^1,2,3,4\)
  – As stated by the ECDC guidance «Similar increase for ProQuad and Priorix Tetra suggesting a class effect »

• No increased risk after the second dose of MMRV demonstrated with ProQuad \(^4,5\)

• National recommendations for use of MMRV were revised in the US, Italy, Greece and Germany\(^4\)

Varicella-containing vaccines safety profile in Italy

**Canale Verde** (Green Channel) adverse events surveillance system

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Serious AE per 10,000 doses&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR+V&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.2</td>
</tr>
<tr>
<td>MMRV (<em>Priorix-Tetra</em>)</td>
<td>3.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> = 1,240 reports; <sup>b</sup> Taking into account co-administered doses; <sup>c</sup> MMR vaccine: MMRVAXPRO™ (SPMSD) or Priorix™ (GSK). Varicella vaccine: Varivax™ (Merck) or Varilrix™ (GSK). MMR+V, measles–mumps–rubella vaccine plus separate varicella vaccine; MMRV, measles–mumps–rubella–varicella vaccine.

Incidence rates of febrile convulsions at pediatric age (0-14 years), Italy - 2006-2010

The additional febrile convulsions that would occur according to the BIPS study using MMRV instead of MMR+V would be 20-30/100,000 in the 2nd year of life on a baseline rate of 1047/100,000 hospitalized seizures cases due to other causes.

Herpes zoster vaccines and vaccination
HZ incidence in Europe is about 3-4 per 1000 person-years. It is highly age-dependent.

- Studies conducted in Europe estimate an overall annual incidence of HZ of 2.0-4.6 cases per 1000 persons [Pichinat 2013]. **HZ incidence rates appeared to increase rapidly after 50 years to around 7–8/1 000 up to 10/1 000 at 80 years of age and older**

- According to a US large retrospective population study [Yawn 2007] incidence ranges from 4.2 per 1000 person-years in people aged 50 to 59 years and 10.7 per 1000 person-years in people aged 80+ years.

In the European population ≥50 years:

- ≥ 1.7 M new cases per year (7-8/1,000 in ≥50 years, up to 10/1,000 in ≥80 years)
- about 20% complicated by PHN: ≥ 260,000 cases per year

Pichinat 2013: Country specific data are available for Belgium, France, Germany, Iceland, Italy, the Netherlands, Spain, Switzerland and UK.
This study confirms an average 65% effectiveness against PHN in all age groups, in line with several recent and previous studies.
HZ/su - Vaccine Composition

Vaccine Non-live

Antigen
Glycoprotein E (gE) - 50 µg

Adjuvant System
AS01b (MPL and QS-21*) - 50 µg each

* QS-21 (Quillaja saponaria Molina; fraction 21; licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
# ZOE-50 Study

## Vaccine Efficacy Overall & by Age Group

### Modified Total Vaccinated Cohort (mTVC)*

*Excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>HZ cases</th>
<th>Rate of HZ (Number per 1000 Person-Years)</th>
<th>HZ cases</th>
<th>Rate of HZ (Number per 1000 Person-Years)</th>
<th>VE (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (≥50)</td>
<td>6</td>
<td>0.3</td>
<td>210</td>
<td>9.1</td>
<td>97.2 (93.7-99.0)</td>
</tr>
<tr>
<td>50-59</td>
<td>3</td>
<td>0.3</td>
<td>87</td>
<td>7.8</td>
<td>96.6 (89.6-99.3)</td>
</tr>
<tr>
<td>60-69</td>
<td>2</td>
<td>0.3</td>
<td>75</td>
<td>10.8</td>
<td>97.4 (90.1-99.7)</td>
</tr>
<tr>
<td>≥70</td>
<td>1</td>
<td>0.2</td>
<td>48</td>
<td>9.4</td>
<td>97.9 (87.9-100)</td>
</tr>
<tr>
<td>≥60²</td>
<td>3</td>
<td>0.2</td>
<td>123</td>
<td>10.2</td>
<td>97.6 (92.8-99.6)</td>
</tr>
</tbody>
</table>


*Excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2

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# ZOE-70 Study

## Vaccine Efficacy Against HZ Overall & by Age Group

### Modified Total Vaccinated Cohort (mTVC)

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>HZ cases</th>
<th>Rate of HZ (Number per 1000 Person-Years)</th>
<th>HZ cases</th>
<th>Rate of HZ (Number per 1000 Person-Years)</th>
<th>VE (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (≥70)</td>
<td>23</td>
<td>0.9</td>
<td>223</td>
<td>9.2</td>
<td>89.8 (84.2-93.7)</td>
</tr>
<tr>
<td>70-79</td>
<td>17</td>
<td>0.9</td>
<td>169</td>
<td>8.8</td>
<td>90.0 (83.5-94.4)</td>
</tr>
<tr>
<td>≥80</td>
<td>6</td>
<td>1.2</td>
<td>54</td>
<td>11.0</td>
<td>89.1 (74.6-96.2)</td>
</tr>
</tbody>
</table>

*P-value for all efficacy comparisons with placebo <0.001

RZV: Recommended by the United States CDC for the prevention of shingles*

The CDC states that RZV is:

- Recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years
- Recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL)
- Preferred over ZVL for the prevention of herpes zoster and related complications

Centers for Disease Control and Prevention. MMWR. Morb Mortal Wkly Rep 2018;67:103-108. DOI Link: http://dx.doi.org/10.15585/mmwr.mm6703a5
RZV: Recommended by the German Standing Committee on Vaccination (STIKO)

STIKO recommends adjuvanted herpes zoster vaccine as the standard vaccine

- As general vaccination for prevention of herpes zoster and its complications for persons over the age of 60 years

- For persons over the age of 50 years with immunocompromising condition or with severe underlying disease.

  - For example: congenital or acquired immunodeficiency or immunosuppression; HIV; rheumatoid arthritis, systemic lupus erythematosus, chronic inflammatory bowel disease, chronic obstructive pulmonary disease or bronchial asthma, chronic renal insufficiency, diabetes mellitus
TO THE EDITOR—Harpaz [1] argues that what has, and has not, taken place in the United States, even if it does not quite yet allow theoretical concerns about reduced exogenous boosting following universal varicella vaccine introduction to be completely ignored, ought at the very least to provoke some revision of the models being used to estimate the timing, size, and duration of any such rise. After all, at some point, real life must surely trump prophecy? Van Hoek [1] chooses instead to continue to argue that exogenous boosting may actually matter and proposes that it may help explain rises in zoster occurring both in the absence of vaccination and following it—although he does not offer an explanation as to why, in that case, notional vaccine-induced effects replaced the effects occurring prior to vaccination but did not augment them, nor why more recent US data suggest that the rise, far from accelerating, appears to have stopped at the very time the models would have had them taking off.

But, perhaps because the scope of the paper does not extend beyond Hope-Simpson's exogenous hypothesis, neither author points out that it invokes a theoretical problem to which we already have a solution. Live attenuated zoster vaccine, while effective [2], may provide only temporary and partial protection and cannot be used in some elderly people who are at the highest risk. However, available evidence suggests strongly that the recently licensed nonlive adjuvanted vaccine overcomes these limitations [3]. Surely it is time for policymakers to stop imagining that they have to continue to permit much preventable morbidity to occur in children in order to protect adults from zoster, when they can use zoster vaccine to do the job instead?
Conclusions (1)

- Varicella is a very frequent disease. Although it is generally benign, the burden of disease is considerable.
- The awareness of such burden is often insufficient in HCWs, policy makers and the population.
- The available vaccines are efficacious, effective and safe.
- Cost-effectiveness studies almost invariably show that, if the impact on zoster in the long term is not considered, universal vaccination is very cost-effective and often cost-saving.
- The prophesized increase of zoster as a consequence of universal varicella vaccination has never been demonstrated in reality.
- Primary vaccine failure seems to play a more relevant role than secondary failure as a determinant for breakthrough infections.
Conclusions (2)

• However, coverage is the most important factor in impacting varicella reduction (compared to effectiveness and interval between doses)

• Herpes zoster has a high disease burden in the elderly population

• ZVL has a 65% effectiveness in the prevention of PHN, RZV has >90% efficacy against Herpes zoster. Higher coverage needed

• The new vaccine can avoid (if used) any possible increase of zoster as a consequence of varicella universal immunization (should Hope-Simpson hypothesis be correct..)

• It is time to push health authorities in each country to seriously consider recommending universal children vaccination + catch up of susceptible adolescents, and increasing recommendations and coverage with Herpes zoster vaccine
Knowing is not enough, we must apply,
Willing is not enough, we must do

J.W. Goethe

Thank you for your attention!
Varicella vaccination perception

Decision-makers perception: varicella not a severe disease

‘Chickenpox parties’

Aim to give children the disease when very young

Belief that children are then immunised (for life?)

Supranational authorities recommendations

WHO recommends\(^1\)
- One dose
  - To reduce mortality and severe morbidity
- Two doses
  - To reduce cases and outbreaks
  - For defined risk groups e.g. immunocompromised individuals and healthcare workers

Europe\(^2\)
- ECDC gives guidance on a two-dose vaccination schedule
- Recommendations vary by country

One-dose schedules effectively control severe disease, albeit with mild breakthrough disease.

Two-dose schedules provide optimal protection to the individual and have the potential to eliminate disease and reduce breakthrough varicella\(^1,3\).
MMRV impact on two-dose strategy, Germany (1)

Varicella vaccination coverage decreased in some regions of Germany when MMR+V was recommended as the first dose instead of MMRV.

The change in recommendations was in response to observations of increased FCs following a first dose of MMRV. Mann-Whitney U-test. FC, febrile convulsion; MMR, measles, mumps, rubella; V, varicella. Streng A & Liese JG. Vaccine 2014;32:897–900.
In 2013, monovalent V vaccine doses DO NOT compensate for the reduction of number of doses of quadrivalent MMRV.
Varicella vaccination short vs long schedule

Short-term interval
- ≥1month -

- Better compliance and coverage depending on:
  - Existing vaccination schedule
  - Particular healthcare system

- Clear evidence of efficacy and immunogenicity from clinical trials and effectiveness from real-life data²

- Reduced risk of breakthrough varicella and outbreaks based on coverage with short vs long schedule¹

Long-term interval

- --- years ---

- Easily paired to MMR vaccination programs³

- Easier to implement when paired to a compulsory school program³ (e.g. US second dose)

- Evidence of effectiveness from real-life data⁴

- Minimize risk of waning immunity² and help protect adolescents/adults when the disease can be more severe

Age-shift of varicella onset in 1995 and 2004

All absolute numbers are lower in 2004 vs 1995, when URV was introduced