Le Vaccinazioni nel Paziente Ematologico:
scontro tra Immuno-attivazione e Immuno-depressione

*15 Ottobre 2016*

# *Raccomandazioni per i Pazienti Ematologici: rischi e benefici*

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Rene Magritte – Golconda, 1953

Salvador Dalì – La persistenza della memoria, 1931

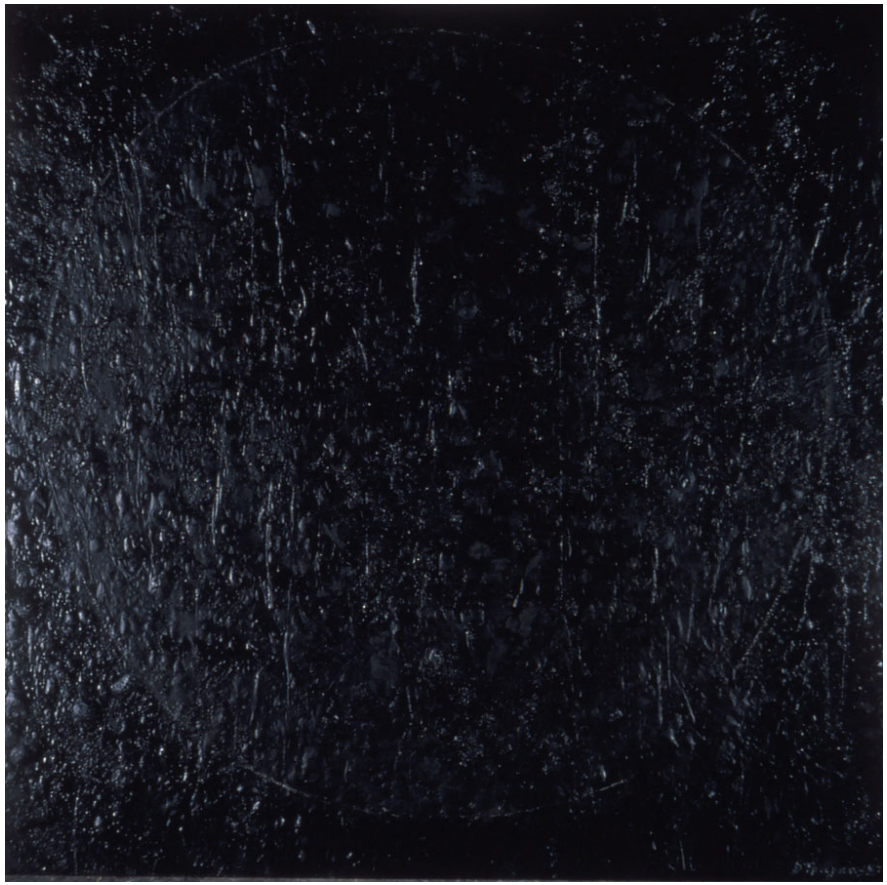
# Background

- Patients with hematological malignancies are at high risk of infections that are potentially preventable by vaccinations
- Immunosuppressed individual have very high morbidity and mortality related to infections because are unable to mount a protective immune response to active vaccination
- Antimicrobial therapy in immunosuppressed patients is often less effective than in the unimpaired host

# Caveat

No true efficacy data exist and the recommendations are mainly based on safety and immuneresponse.

Dimitris Tragkas – Circle, 1988



# Key Point

- Who and With What ?
- When ?
- Why (efficacy) ?
- How much ?

# WHO & WITH WHAT ?

Vaccinations in patients with hematological malignancies.

| Vaccine | When[a] | Recommendations |
|---|---|---|
| PCV13 followed by PPSV23 | Before therapy | Indicated in lymphoma, myeloma, and CLL patients if possible |
| | After therapy | Response to vaccination is poor for at least 6–12 months after treatment with anti-B cell antibodies. Unclear if repeated doses of PCV13 are beneficial. |
| Inactivated influenza vaccine | Before therapy | Likely to be beneficial although studies are lacking |
| | After therapy | Administer annually to all patients<br>Intensive immunosuppressive therapy will decrease response to vaccination<br>Anti-B-cell antibody therapy suppresses response to vaccination for 6–12 months |
| Varicella vaccine | Before therapy | Negative risk – benefit ratio in patients with active disease[b] |
| | After therapy | For patients in remission, administer no earlier than 3 months after completion of chemotherapy and at least 12 months after anti-B-cell antibody therapy |
| Zoster vaccine | Before therapy | Negative risk – benefit ratio in patients with active disease[b] |
| | After therapy | For patients in remission, administer no earlier than 3 months after completion of chemotherapy and at least 12 months after anti-B-cell antibody therapy |
| MMR | Before therapy | Negative risk – benefit ratio in patients with active disease[b] |
| | After therapy | Seronegative adults depending on the local epidemiological situation. For patients in remission, administer no earlier than 3 months after completion of chemotherapy and at least 12 months after anti-B-cell antibody therapy |
| Travel vaccines | After therapy | Efficacy of inactivated vaccines (e.g. hepatitis, poliovirus, diphtheria) are unclear, although they lack risks<br>Live vaccines (e.g. yellow fever) have unclear efficacy and safety |

Recommendations for vaccinations in hematopoietic stem cell transplant (HSCT) patients.

| Vaccine | When | Comments |
|---|---|---|
| Tetanus toxoid + diphtheria toxoid | Before transplantation | Not indicated |
| | After transplantation | Three doses (DT) starting at 6–12 months after transplantation |
| Inactivated poliovirus + pertussis | Before transplantation | Not indicated |
| | After transplantation | Three doses starting at 6–12 months after transplantation |
| Inactivated influenza | Before transplantation | Might result in improved transfer of immunity |
| | After transplantation | Annually beginning 4–6 months after transplantation depending on season |
| Pneumococcal conjugate | Before transplantation | Can improve transfer of immunity |
| | After transplantation | Three doses starting 3–6 months after transplantation. Booster at 12 months for patients with chronic graft-vs-host disease (GVHD) |
| Pneumococcal polysaccharide | Before transplantation | Not effective |
| | After transplantation | After three doses of pneumococcal conjugate vaccine have been given, administer pneumococcal polysaccharide booster at 12 months for patients without GVHD |
| Conjugated *H. influenzae* group B | Before transplantation | Can improve transfer of immunity |
| | After transplantation | Three doses starting 3–6 months after transplantation. Booster at 12 months for patients with chronic GVHD |
| Papilloma virus | Before transplantation | No data |
| | After transplantation | No data, but recommended starting at 6 months if not current with recommendations |
| Varicella vaccine | Before transplantation | Seronegative patients at least 4 weeks before start of conditioning |
| | After transplantation | Seronegative patients, not before 24 months after HSCT; not to be given to patients with GVHD or ongoing immunosuppression |
| Zoster vaccine | Before transplantation | No data |
| | After transplantation | Not recommended |
| MMR | Before transplantation | Seronegative patients at least 4 weeks before start of conditioning |
| | After transplantation | Not before 24 months after HSCT; not to be given to patients with GVHD or ongoing immunosuppression |
| Travel vaccines | After transplantation | Inactivated vaccines are likely to have positive risk – benefit ratio.<br>Live vaccines - not before 24 months after HSCT; not to be given to patients with GVHD or ongoing immunosuppression |

Tsigrelis C & Ljungman. *Blood Reviews* 2016. 30:139-147

# Type of Vaccines Recommended in Cancer Patients IDSA and NCCN

| Patients | Vaccine | Timing | Number of doses |
|---|---|---|---|
| **Hematological malignancies** | • ***Inactivated-Influenza*** | Annually* | 1 |
| | • ***Conjugated 13-valent*** | Before therapy* | 1-2 |
| | • ***Polysaccharide 23*** | 8 weeks later | 1 |
| **HSCT** | • ***Inactivated-Influenza*** | Annually** | 1 |
| | • ***Conjugated 13-valent*** | 3-6 months*** | 3**** |
| | • ***Polysaccharide 23*** | ≥ 12 months*** | 1 |
| **Household menbers** | • ***Inactivated-Influenza*** | Annually | 1 |

*Intensive immunosoppressive therapy will decrease response to vaccination; anti-B-cell antibody therapy suppresses response to vaccination for 6-12 months
**from 4-6 months from transplant
***from transplant
****booster at 12 months if cGVHD

# Live-Attenuated *vs.* Inactivated Influenza Vaccine

| Factor | Live-attenuated | Inactivated |
|---|---|---|
| **Recommended 2016-2017** | No | Yes |
| **Route of administration** | Intranasal spray | Intramuscolar injection |
| **Type of vaccine** | Live virus | Killed virus |
| **Updated** | Annually | Annually |
| **Approved age** | From 2 to 49 years | From 6 months |
| **Can be given to persons with risk factors for flu complications? *** | No | Yes |
| **Can be administered to close contacts of immunosuppressed persons not requiring a protected environment?** | Yes | Yes |
| **Can be administered to close contacts of immunosuppressed persons requiring a protected environment?** | No | Yes |
| **Can be administered simultaneously with other vaccines?** | Yes | Yes |

* Chronic diseases involving lung, heart, kidneys, liver, CNS, PNS, hematology, metabolism

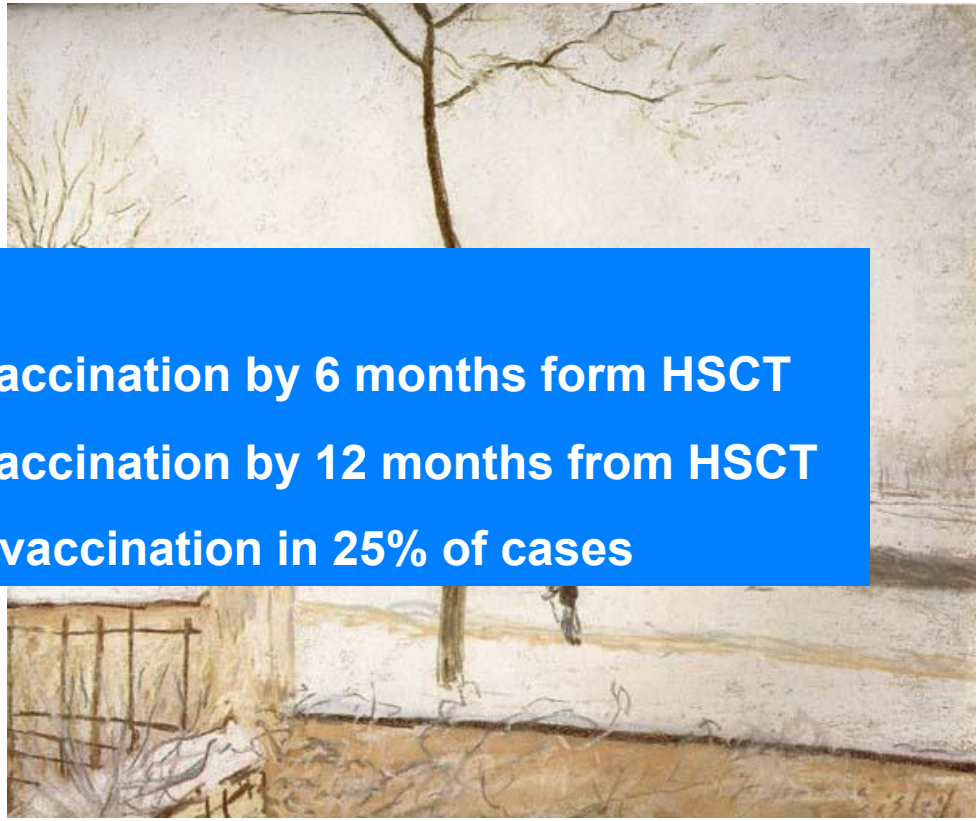
Grohskopf LA et al. *MMWR Morb Mortal Wkly Rep* 2015; 64:818.
Centers for Disease Control and Prevention. (June 24, 2016).

# Vaccination for Pneumococcal Infection: Patients with Cancer (Infectious Diseases Society of America)

| | |
|---|---|
| **Conjugate Vaccines (7 and 13-valent)** | ***Usual administer*** 1 dose PCV 13 at diagnosis<br>[Strength: *strong*; Evidence quality: very *low*]<br><br>**More immunogenic (T-cell dependent), covers few serotype** |
| **Polysaccharide Vaccines (14 and 23-valent)** | ***Usual administer*** 8 weeks after PCV 13<br>[Strength: *strong*; Evidence quality: *low*]<br><br>**Poorly immunogenic (T-cell independent), covers more serotypes** |

Rubin LG et al. *Clin Infect Dis*. 2014;58(3):e44.
Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep. 2013;62(RR-07):1.

# Real life

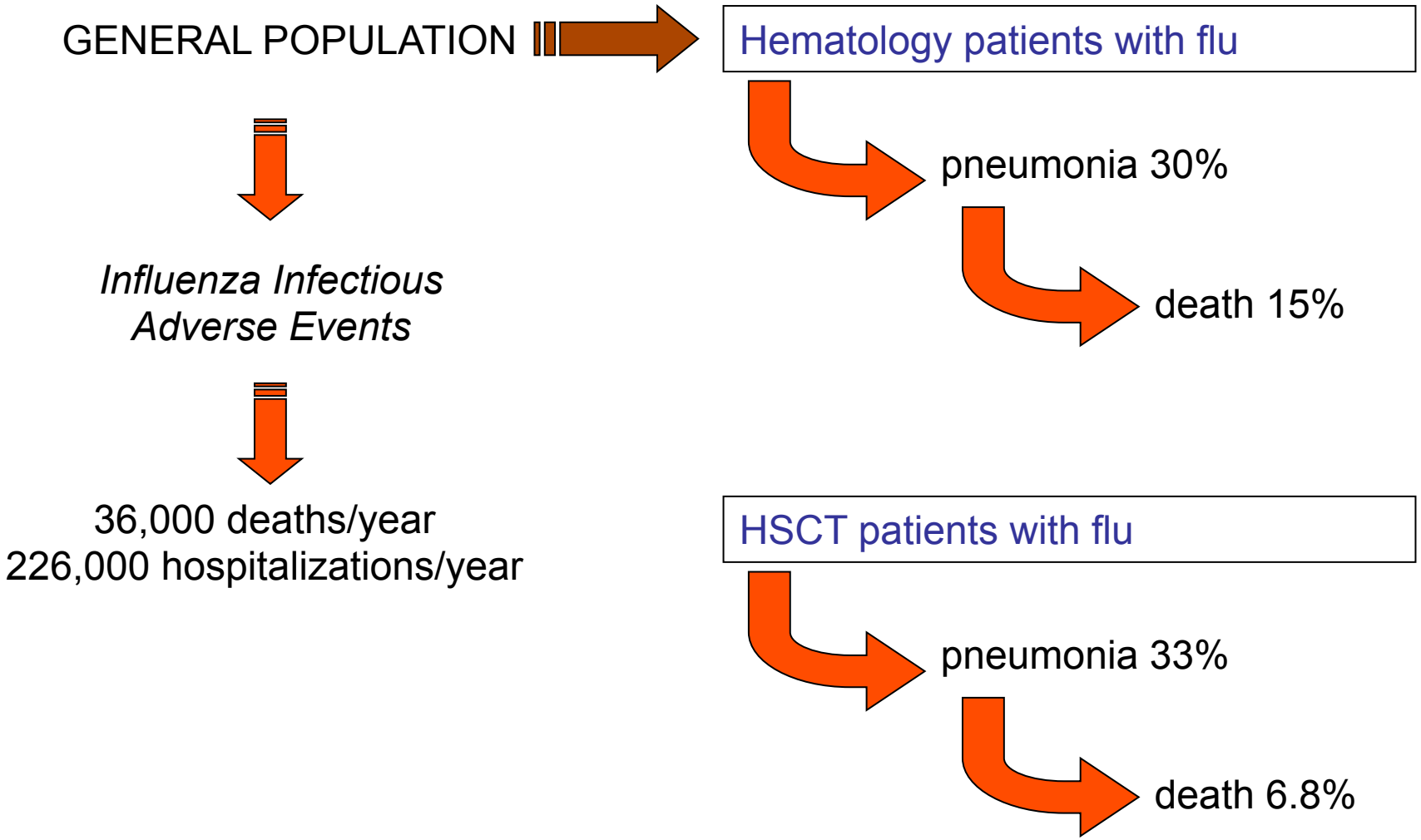



*MD Anderson CC 2010-2013*:

- **38% of patients have received vaccination by 6 months form HSCT**
- **60% of patients have received vaccination by 12 months from HSCT**
- **no clear reason for withholding vaccination in 25% of cases**

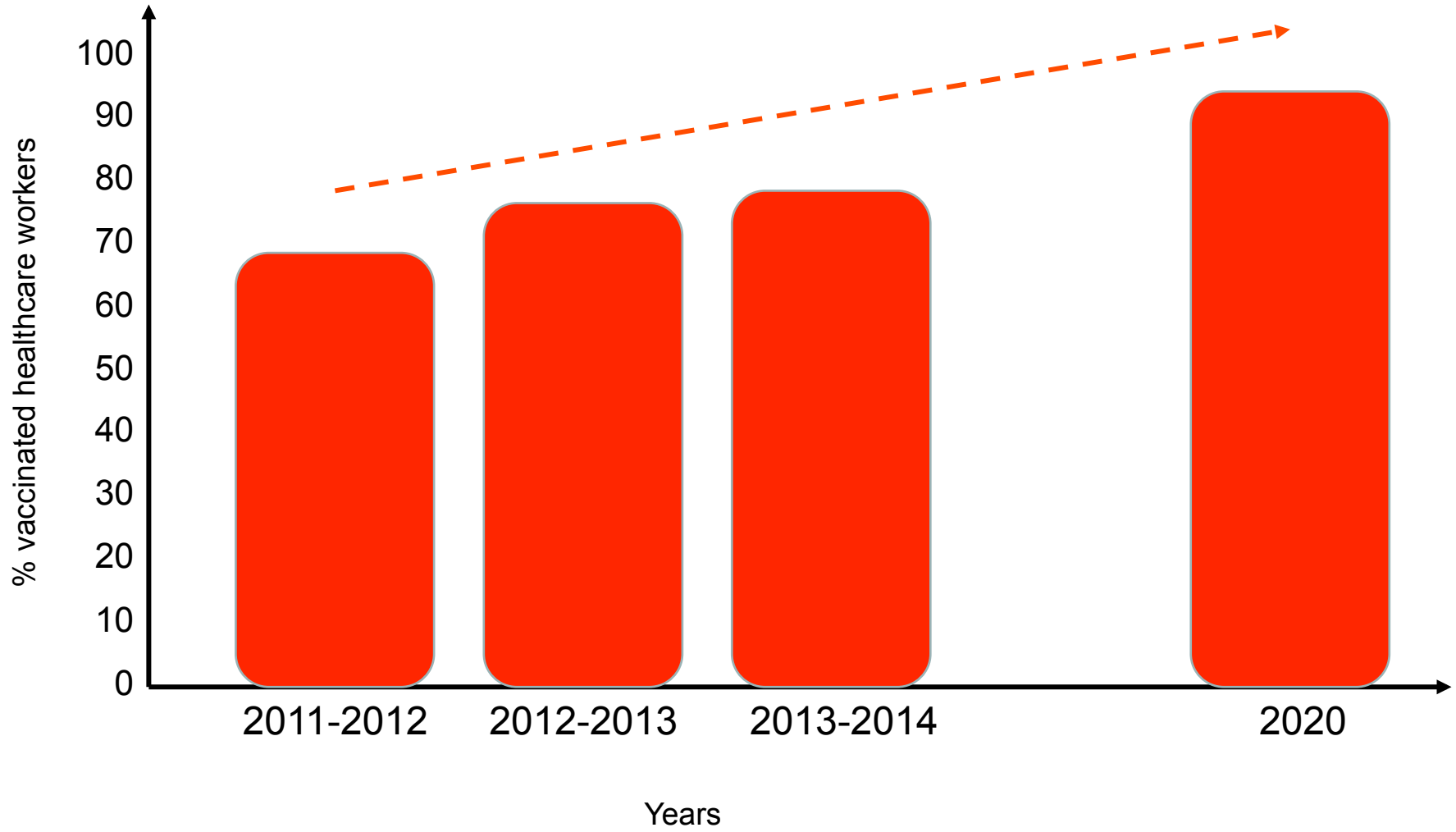
Rubin LG et al. *Clin Infect Dis*. 2014;58(3):e44.
Shehata MA et al. *Clin Med In Onc*. 2014:8
Fiore AE et al. *MMWR Recomm Rep*. 2007;56:1-54
Centers for Disease Control and Prevention. (2010-2011)
Tsigrelis C & Ljungman. *Blood Reviews* 2016. 30:139-147.
Lerchenfeldt SM et al. *Transpl Infect Dis*. 2013;15:634-8.

# Hematology Patients and Influenza




Chemaly RF et al. *Medicine*. 2006;85:278.
Ljungman P et al. *Hematologica*. 2011;96:1231-1235.

# Mandatory Flu Shot Policy for Healthcare Workers



# WHEN ?

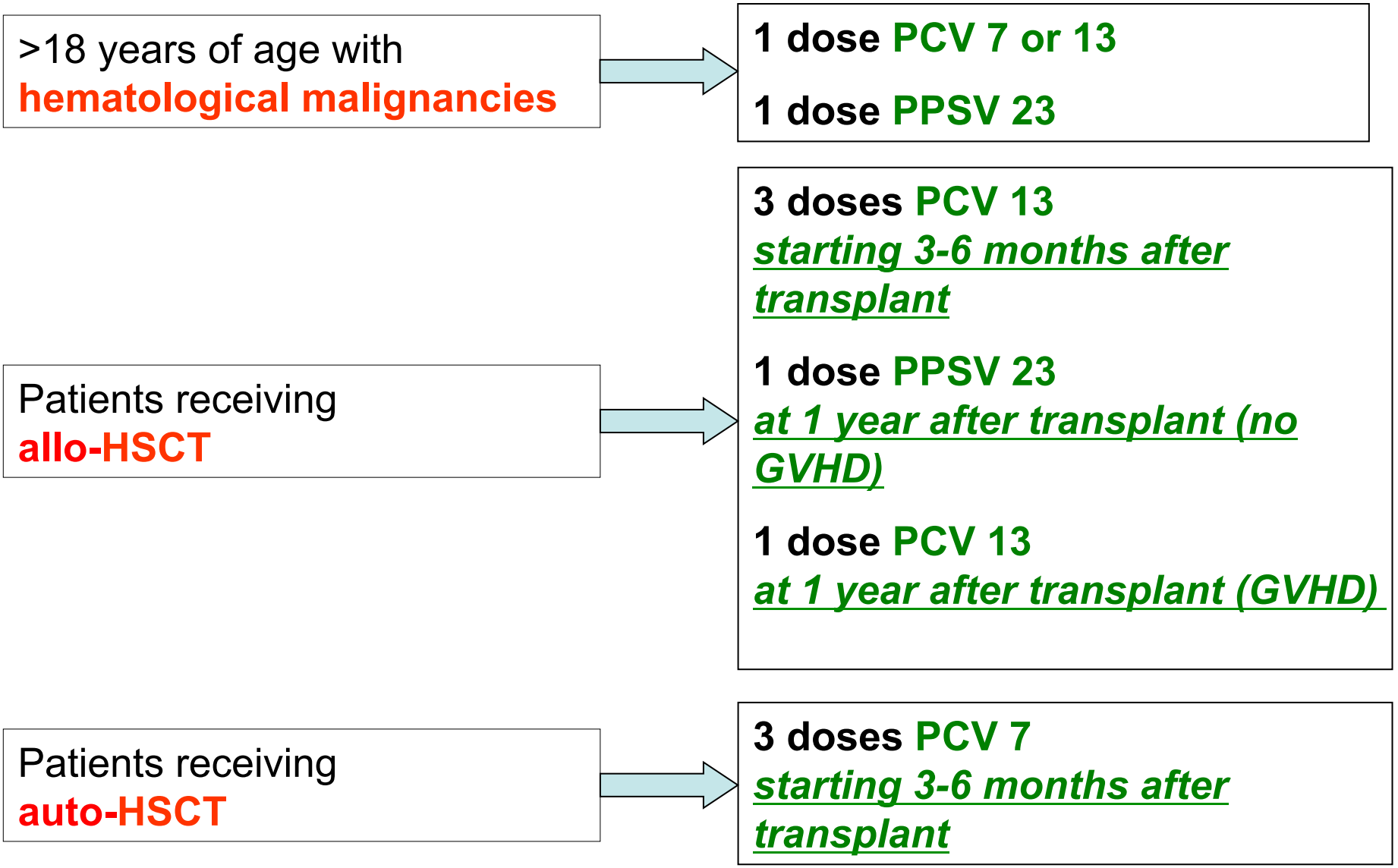
# Timing of Imunization for Influenza Vaccine

## Late fall to early spring

| | | |
|---|---|---|
| ≥ 6 months of age with **hematological malignancies (also intensive cht)** | → | **inactivated influenza vaccine** ***annually (2 wks prior, during, or 3 months after cth)*** |
| Patients receiving **HSCT** | → | **inactivated influenza vaccine** ***2 wks before or 6 months after HSCT (4 months if community outbreak occurs)*** |
| Patients receiving **anti-B cell Abs** | → | **inactivated influenza vaccine** ***delay for 6 months from end of treatment*** |


Rubin LG et al. *Clin Infect Dis*. 2014;58(3):e44.
Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep. 2013;62(RR-07):1.
Tsigrelis C & Ljungman. *Blood Reviews* 2016. 30:139-147.

# Timing of Imunization for Pneumococcal Vaccine




Rubin LG et al. *Clin Infect Dis*. 2014;58(3):e44.
Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep. 2013;62(RR-07):1.
Tsigrelis C & Ljungman. *Blood Reviews* 2016. 30:139-147.

# WHY ?

# Evaluation of the Response

***There is no accepted definition of an adequate serologic response***

**Hemoagglutinin Inhibition Assay to determine antibody titre against influenza virus:**

| | | |
|---|---|---|
| **Vaccination Response** | *Seroconversion* | Four-fold titre increase (at least) |
| **Influenza Immunity** | *Seroprotection* | Anti-Hemoagglutinin Inhibition titre ≥ 40 (Antibodies) |

# Efficacy of Influenza Vaccination in Hematology

12 studies comparing immuneresponse in patients

**RECEIVING CHEMOTHERAPY** *versus* **NOT RECEIVING CHEMOTHERAPY** *versus* **HEALTHY ADULTS**

1. Lymphoma (n=29) **3%** vs 24%
2. Lymphoma (n=29) **30-40%** vs 96%
3. Myeloma (n=48) **19%** (differe

Weaker response in adult receiving chemotherapy

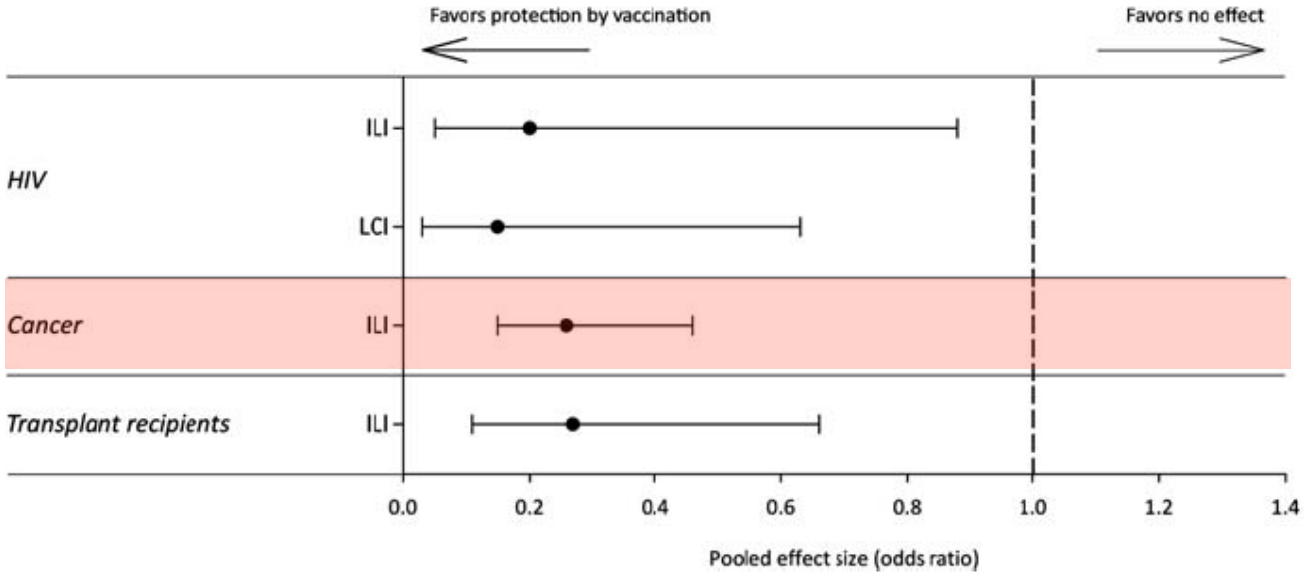
4. (n=23) **17%** vs 93%
(n=25) **36%** vs 82%
ma (n=41) **42-50%**
phoma (n=34) **76-62-65%** vs 82-97-97% (different strains)
8. Lymphoma (n=32) **59-69%** vs 91-97%
9. CLL (n=43) **56%** vs 100%
10. Hematology (n=70) **21-26-16%** (different strains)
11. Hematology (n=31) **32-52%** vs 56-78% (different strains)
12. Hematology (n=21) **67%** vs 94%

Shehata MA et al. *Clinical Medicine Insights: Oncology*. 2014;8:57-64

# Serological and Clinical Influenza Outcome in Patients with Cancer (England-Swizzerland)

| Outcome Measure | Influenza Subtype | Comparator | Studies Included, No. | Pooled ES (95% CI) | *P* for ES | $I^2$ (%) | *P* for $I^2$ |
|---|---|---|---|---|---|---|---|
| Patients with cancer | | | | | | | |
| SC1 | A(H1N1) (S) | VICT | 12[a] | 0.31 (.22–.43) | <.001 | 34.8 | NS |
| SC1 | A(H3N2) | VICT | 12[a] | 0.39 (.21–.71) | <.001 | 66.6 | .002 |
| SC1 | B | VICT | 8[a] | 0.37 (.20–.68) | .001 | 46.5 | NS |
| SP | A(H1N1) (S) | VICT | 10[a] | 0.30 (.15–.61) | .001 | 64.3 | .002 |
| SP | A(H3N2) | VICT | 10[a] | 0.30 (.14–.63) | .002 | 62.6 | .003 |
| SP | B | VICT | 9[a] | 0.30 (.14–.67) | .003 | 68.4 | .001 |

**Meta-analysis of influenza-like illness**




Beck CR et al. *JID* 2012;206:150-9

# Serological Outcome in Hematology Patients taking H1N1 vaccine (Canada)

| | Vaccinated ($n=62$) | Unvaccinated ($n=41$) | $p$-Value |
|---|---|---|---|
| Median age [IQR] | 67 [57–74] | 66 [51.5–76] | 0.620 |
| Female, $n$ (%) | 29 (47) | 16 (39) | 0.566 |
| Diagnosis, $n$ (%) | | | 0.908* |
| Acute leukemia | | | |
| Chronic lymphocytic leukemia | | | |
| Chronic myelogenous leukemia | | | |
| Lymphoma | | | |
| Multiple myeloma | | | |
| Myelodysplasia | | | |
| Myeloproliferative neoplasm | | | |
| Other | | | |
| Therapy | | | |
| Past or active chemotherapy | | | |
| Active chemotherapy | | | |
| Past or active rituximab | | | |
| Active rituximab | | | |
| Prior stem cell transplant | | | |
| Serological results | | | |
| Seroconversion (four-fold increase in titer) | 13 (21) | 0 | 0.001 |
| Seroprotection (titer 1:80 or greater) | 25 (40) | 9 (22) | 0.058 |
| Pre-vaccination GMT | 40 ± 22 | 65 ± 113 | 0.957 |
| Pre-vaccination median titer [IQR] | 40 [20–80] | 40 [20–40] | 0.819 |
| Post-vaccination GMT | 73 ± 73 | 69 ± 113 | 0.134 |
| Post-vaccination median titer [IQR] | 40 [20–80] | 40 [20–40] | 0.133 |
| GMTR | 2.2 ± 2.5 | 1.2 ± 0.6 | 0.041 |

| Subgroup | $n$ | Seroconversion | $p$-Value |
|---|---|---|---|
| Age <65 | 25 | 8 (32%) | 0.113 |
| Age ≥65 | 37 | 5 (14%) | |
| Ever chemotherapy | 56 | 10 (18) | 0.100 |
| Never chemotherapy | 6 | 3 (50) | |
| Active chemotherapy | 46 | 10 (22) | 1.00 |
| No active chemotherapy | 16 | 3 (19) | |
| Ever rituximab | 16 | 2 (13) | 0.484 |
| Never rituximab | 46 | 11 (24) | |
| Active rituximab | 12 | 2 (17) | 1.00 |
| No active rituximab | 50 | 11 (22) | |
| Lymphoid malignancy | 46 | 9 (20) | 0.725 |
| Non-lymphoid malignancy | 16 | 4 (25) | |

Monkman K et al. *Leukemia and Lymphoma* 2011;52(9):1736-1741

# HOW MUCH ?

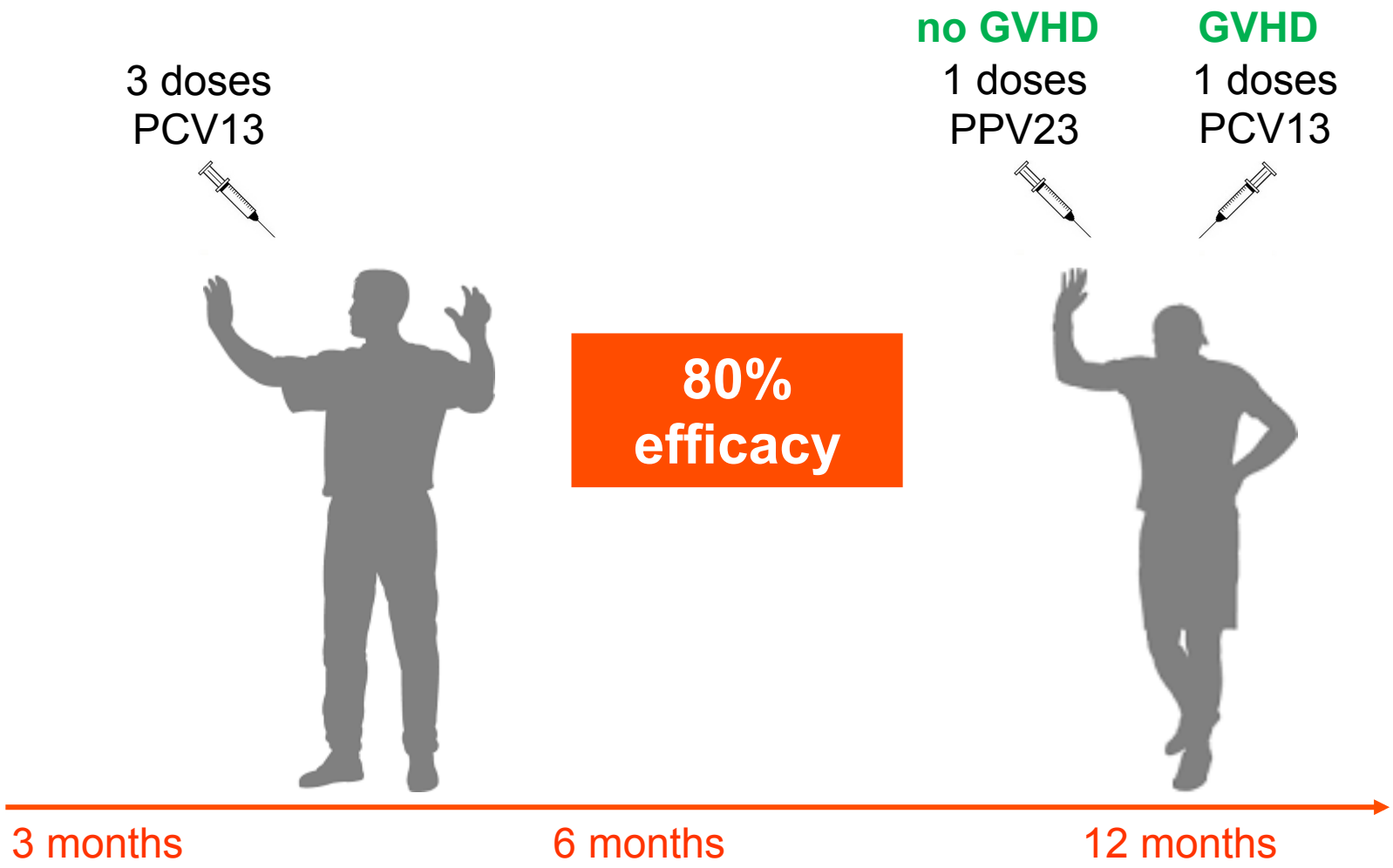
Addition of other doses of vaccine
can improve the response?

# Vaccination for Pneumococcal Infection: Patients with Cancer (Infectious Diseases Society of America)

| | |
|---|---|
| **Polysaccharide Vaccines (PPV 14 and 23-valent)** | Poorly immunogenic<br>Covers more serotypes<br>**LOW RESPONSE RATE IN LEUKEMIA, LYMPHOMA, MYELOMA** |
| **Conjugate Vaccines (PCV 7 and 13-valent)** | More immunogenic<br>Covers few serotype<br>**BETTER RESPONSE RATE IN LEUKEMIA, LYMPHOMA, MYELOMA** |

Rubin LG et al. *Clin Infect Dis*. 2014;58(3):e44.
Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep. 2013;62(RR-07):1.

# Vaccination for Pneumococcal Infection in HSCT



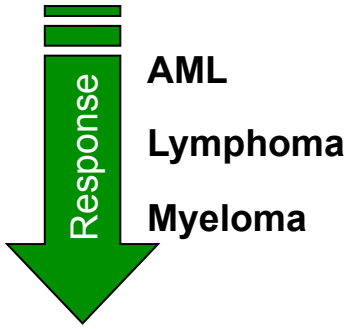
# One or Two Doses for Influenza Vaccine ? (Sweeden)

**Trivalent Influenza Inactivated vaccine**

Interval between the 2 doses was 4 weeks (chemotherapy started after 1 week)

| | Efficacy | H1/N1 | H3/N2 | B |
|---|---|---|---|---|
| **Total** | Response Rate (n=70) | 20% | 20% | 23% |
| | Immunity (n=70) | 21% | 26% | 16% |
| **One Dose** | Response Rate (n=36) | 22% | 14% | 22% |
| | Immunity (n=34) | 18% | 26% | 25% |
| **Two Doses** | Response Rate (n=36) | 26% | 21% | 18% |
| | Immunity (n=34) | 25% | 22% | 14% |

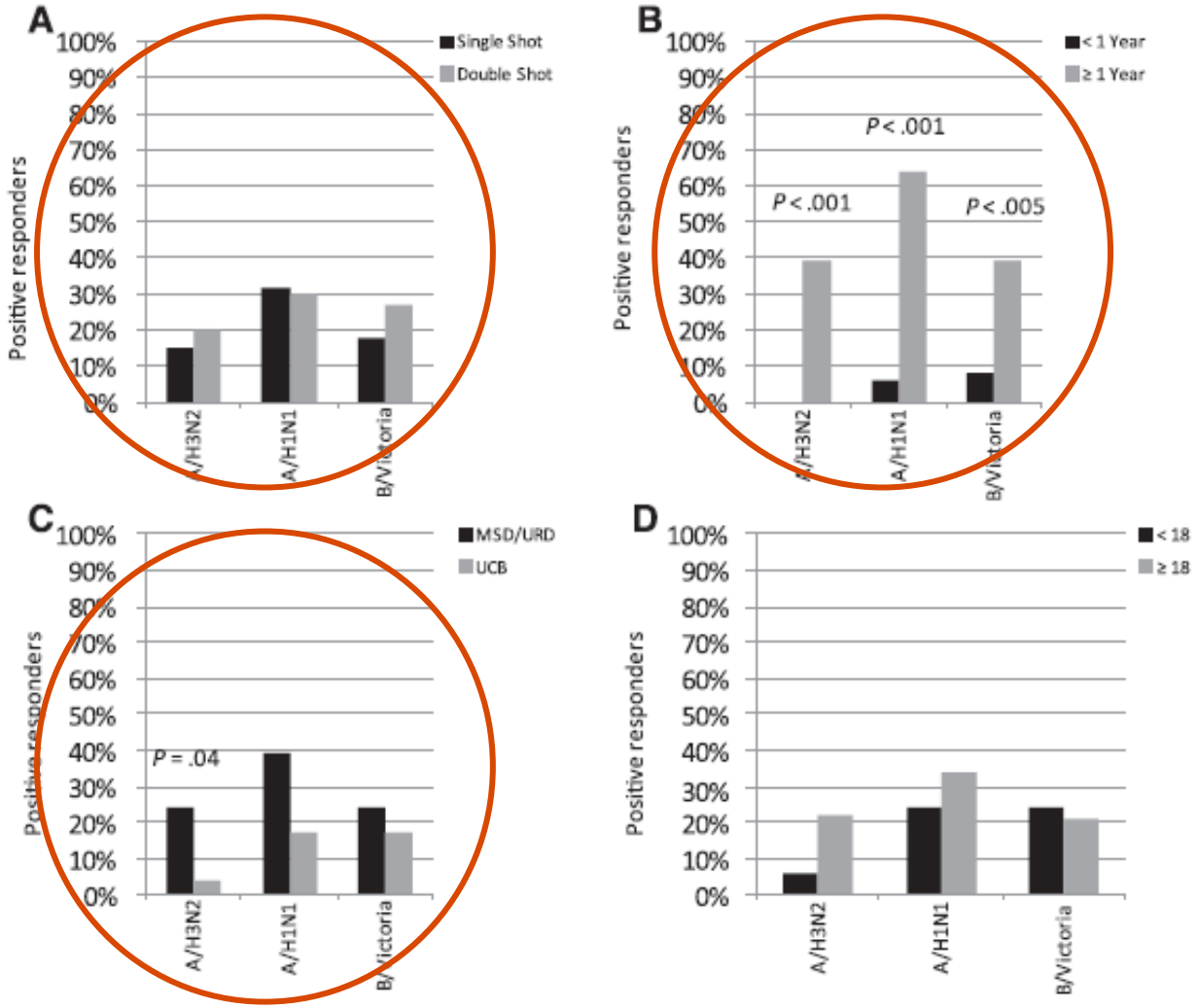
RR = 4-fold HI titre increase
Immunity = HI titre ≥40




Ljungman P et al. *BJH* 2005;130:96-98

# One or Two Doses for Influenza Vaccine ? (USA)

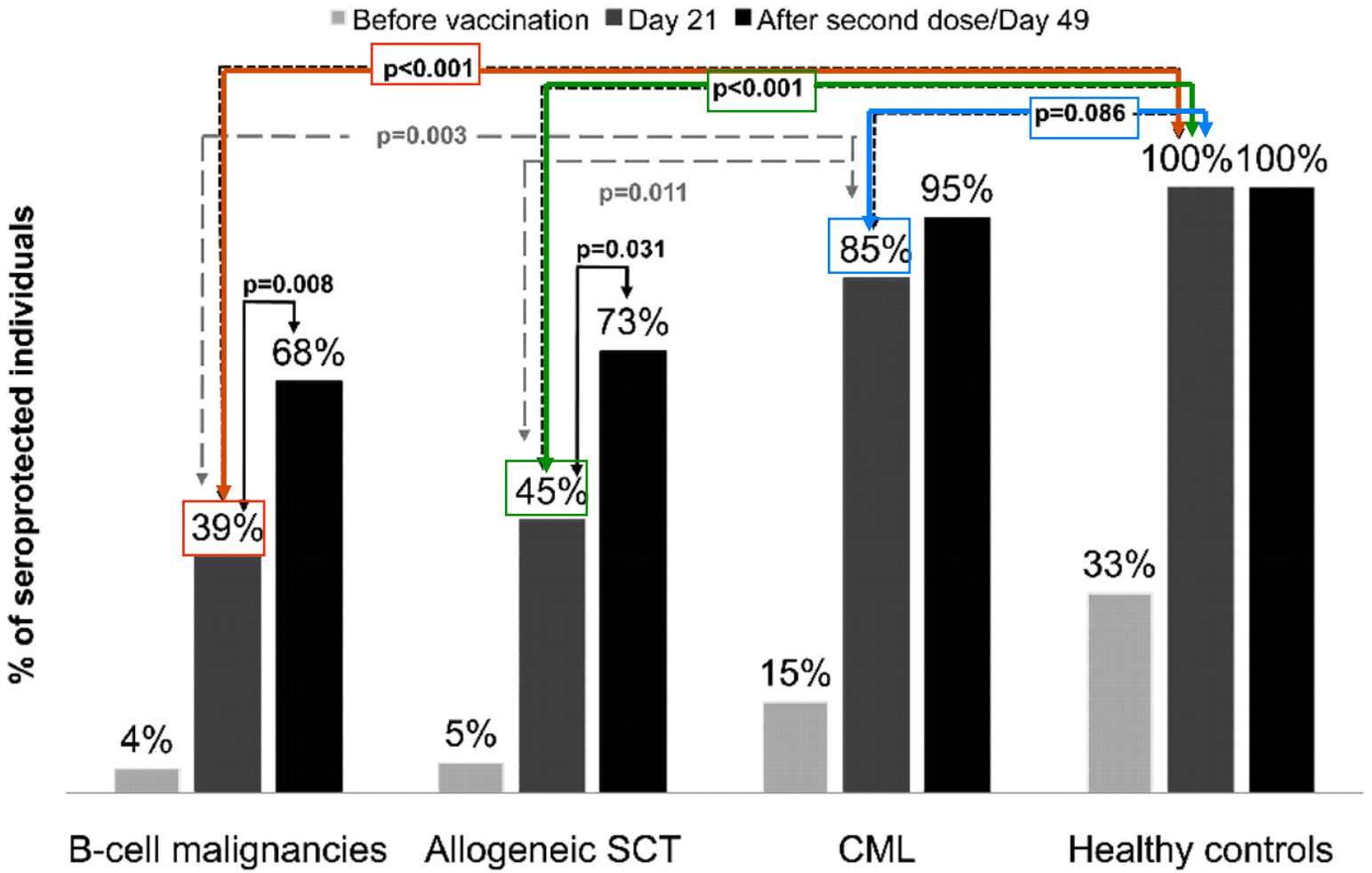
>60 days after HSCT → **FLU VACCINE** → 4 weeks → **FLU VACCINE** observation → 8 weeks → assessment




Karras NA et al. *Biol Blood Marrow Transplant* 2013;19:109-116

# One or Two Doses for Influenza Vaccine ? (England)

Frequency of seroprotected individuals after one dose (97 patients and 25 controls) and two doses (72 patients only) of H1N1 vaccine (adjuvanted)

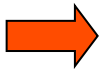



de Lavallade H et al. *Haematologica* 2011;96(2):307-314

# Safety

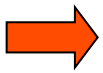
Injection-site and systemic adverse effects within 7 days after the first dose of vaccine among patients.

| Adverse event | Mild | Moderate percent (95% confidence interval) | Severe | All grades |
|---|---|---|---|---|
| Local event | | | | |
| Any | 64.2 (54.6-73.9) | 22.1 (13.8-30.4) | 2.1 (0-5.0) | 88.4 (82.0-94.9) |
| Pain | 54.7 (44.7-64.7) | 18.9 (11.1-26.8) | 1.0 (0-3.1) | 74.7 (66.0-83.5) |
| Tenderness | 57.9 (48.0-67.8) | 20.0 (12.0-28.0) | 2.1 (0-5.0) | 80.0 (72.0-88.0) |
| Redness | 13.7 (6.8-20.6) | 4.2 (0.2-8.2) | 0 | 17.9 (10.2-25.6) |
| Induration | 15.8 (8.5-23.1) | 3.2 (0.4-6.7) | 0 | 18.9 (11.1-26.8) |
| Ecchymosis | 4.2 (0.2-8.2) | 0 | 0 | 4.2 (0.2-8.2) |
| Systemic event | | | | |
| Any | 28.4 (19.4-37.5) | 11.6 (5.1-18.0) | 3.2 (0-6.7) | 43.2 (33.2-53.1) |
| Fever | 5.3 (0.8-9.8) | 3.2 (0-6.7) | 1.1 (0-3.1) | 9.5 (3.6-15.4) |
| Headache | 14.7 (7.6-21.9) | 3.2 (0-6.7) | 0 | 17.9 (10.2-25.6) |
| Malaise | 17.9 (10.2-25.6) | 10.5 (4.4-16.7) | 1.1 (0-3.1) | 29.5 (20.3-38.6) |
| Myalgia | 11.6 (5.1-18.0) | 6.3 (1.4-11.2) | 0 | 17.9 (10.2-25.6) |
| Chills | 6.3 (1.4-11.2) | 3.2 (0-6.7) | 0 | 9.5 (3.6-15.4) |
| Nausea | 7.4 (2.1-12.6) | 1.1 (0-3.1) | 1.1 (0-3.1) | 9.5 (3.6-15.4) |



Controls: 40%

After second shot 8% worsened



Controls: 40%

After second shot 4% worsened

de Lavallade H et al. *Haematologica* 2011;96(2):307-314

# Antibody Responses to H1N1 Influenza Vaccine in Lymphoma Patients: One *vs.* Two Doses

| Sampling time point | Antibody response | One dose (*n* = 20) | Two doses (*n* = 20) | *p*-Value |
|---|---|---|---|---|
| Baseline (day 0) | Seroprotection events (rate) | 1 (5%) | 3 (15%) | 0.292 |
| Second visit (day 21) | Seroconversion events (rate) | 6 (30%) | 1 (5%) | 0.037 |
| | Seroprotection events (rate) | 8 (40%) | 3 (15%) | 0.077 |
| Third visit (day 42) | Seroconversion events (rate) | 6 (30%) | 6 (30%) | 1.0 |
| | Seroprotection events (rate) | 7 (35%) | 8 (40%) | 0.744 |

| Sampling time point | Antibody response | No rituximab (*n* = 26) | Rituximab (*n* = 14) | *p*-Value |
|---|---|---|---|---|
| Baseline (day 0) | Seroprotection events (rate) | 3 (12%) | 1 (7%) | 1.0 |
| Second visit (day 21) | Seroconversion events (rate) | 7 (27%) | 0 | 0.075 |
| | Seroprotection events (rate) | 9 (35%) | 2 (14%) | 0.270 |
| Third visit (day 42) | Seroconversion events (rate) | 10 (39%) | 2 (14%) | 0.157 |
| | Seroprotection events (rate) | 12 (46%) | 3 (21%) | 0.177 |

Villa D et al. *Leukemia & Lymphoma*. 2013;54(7):1387-1395.

# Conclusions….?

- The utility of vaccination in hematology patients is unclear.
- Physician practice vary dramatically.
- Given the risk of severe disease, seasonal influenza vaccination should be recommended.
- Patients and physicians should be aware that vaccination may not confer immunity against influenza.
- It is possible to increase the immunogenicity.
- The inactivated vaccinations in hematology patients are safe.
- Vaccination of close contacts, healthcare workers and good clinical practice are necessary to protect hematology patients.

**“An ounce of prevention is worth a pound of cure.”**

Benjamin Franklin