ASIA FUNGAL WORKING GROUP
an ISHAM working group

Is prophylaxis of *Pneumocystis jiroveci* necessary during use of biologic agents in HIV-uninfected patients ?

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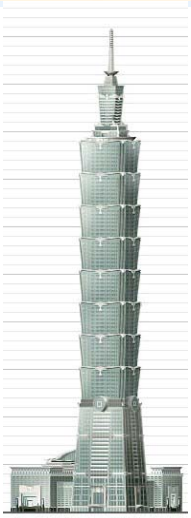
Before the talk…

Have you ever prescribed biologic agents?

Have you encountered opportunistic infection?

I have no conflict of interest

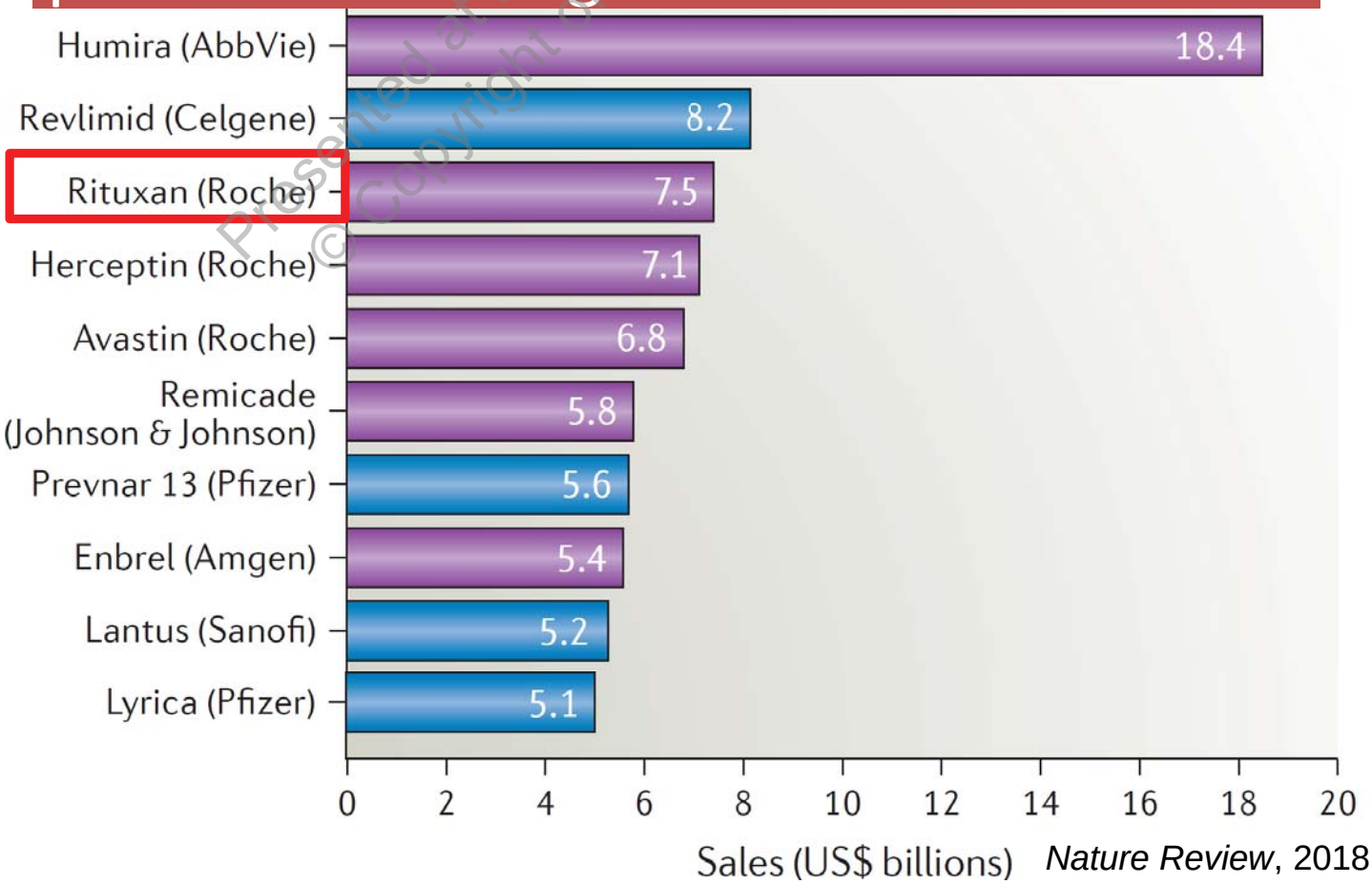


US $ 1.9 billion

US $ 18.4 billion / year

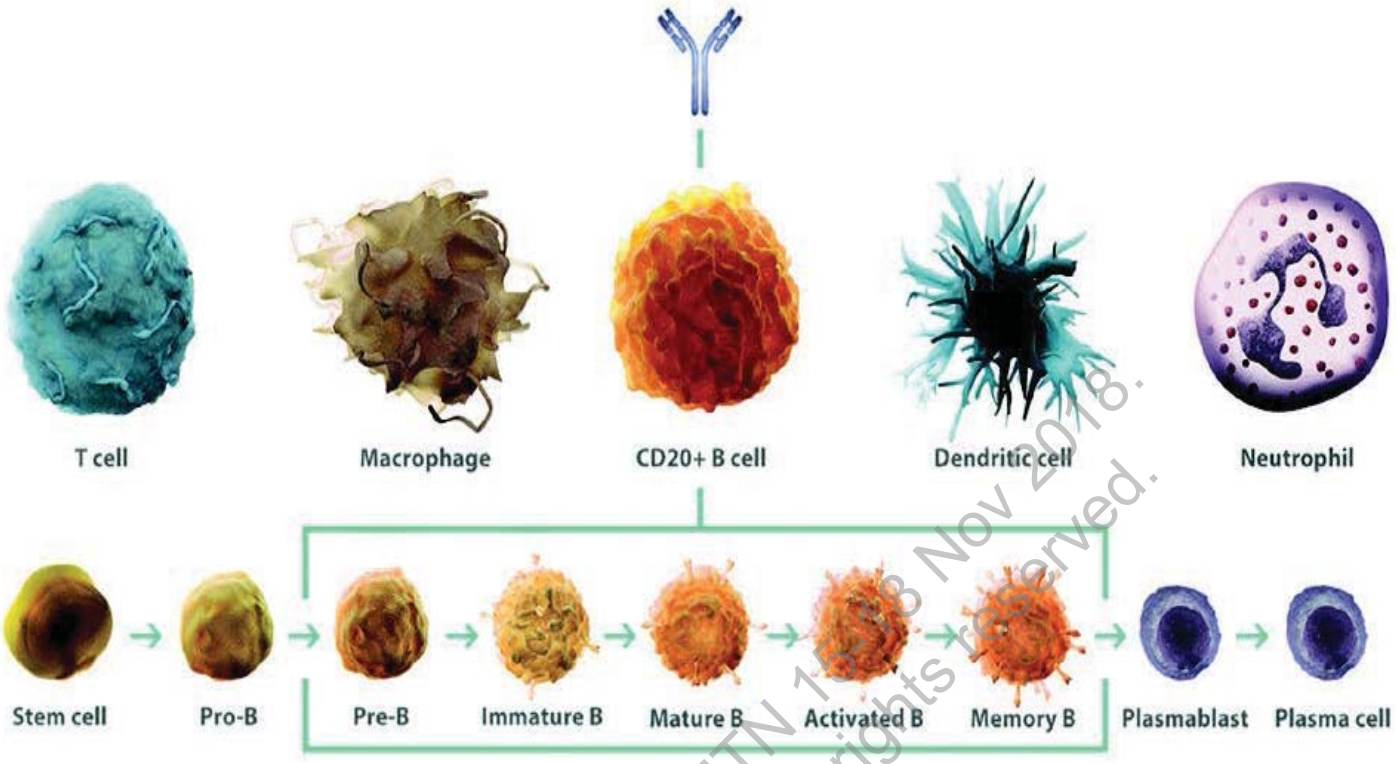
9.4

In perspective, there will be much more patients receiving these treatment



Nature Review, 2018

Rituximab (Rituxan®) (anti-CD20 monoclonal antibody)



List of FDA approved indications

Year	Indication
1997	Non-Hodgkin lymphoma
2006	First line therapy (plus CHOP chemotherapy) for diffuse large B cell lymphoma

In general, biologic agents rarely cause severe opportunistic infection

Era of Biologic Agents

New Hope

New Challenge

~~New~~ Guidelines

Outlines

01 Case sharing

02 *Pneumocystis jiroveci* pneumonia (PJP)

03 non-HIV with PJP

04 Prophylaxis

Outlines

01 Case sharing

02 *Pneumocystis jirovecii*

03 non-HIV

04 Prophylaxis

61 year-old man
Pemphigus vulgaris (PV)

PV stable for 1 year

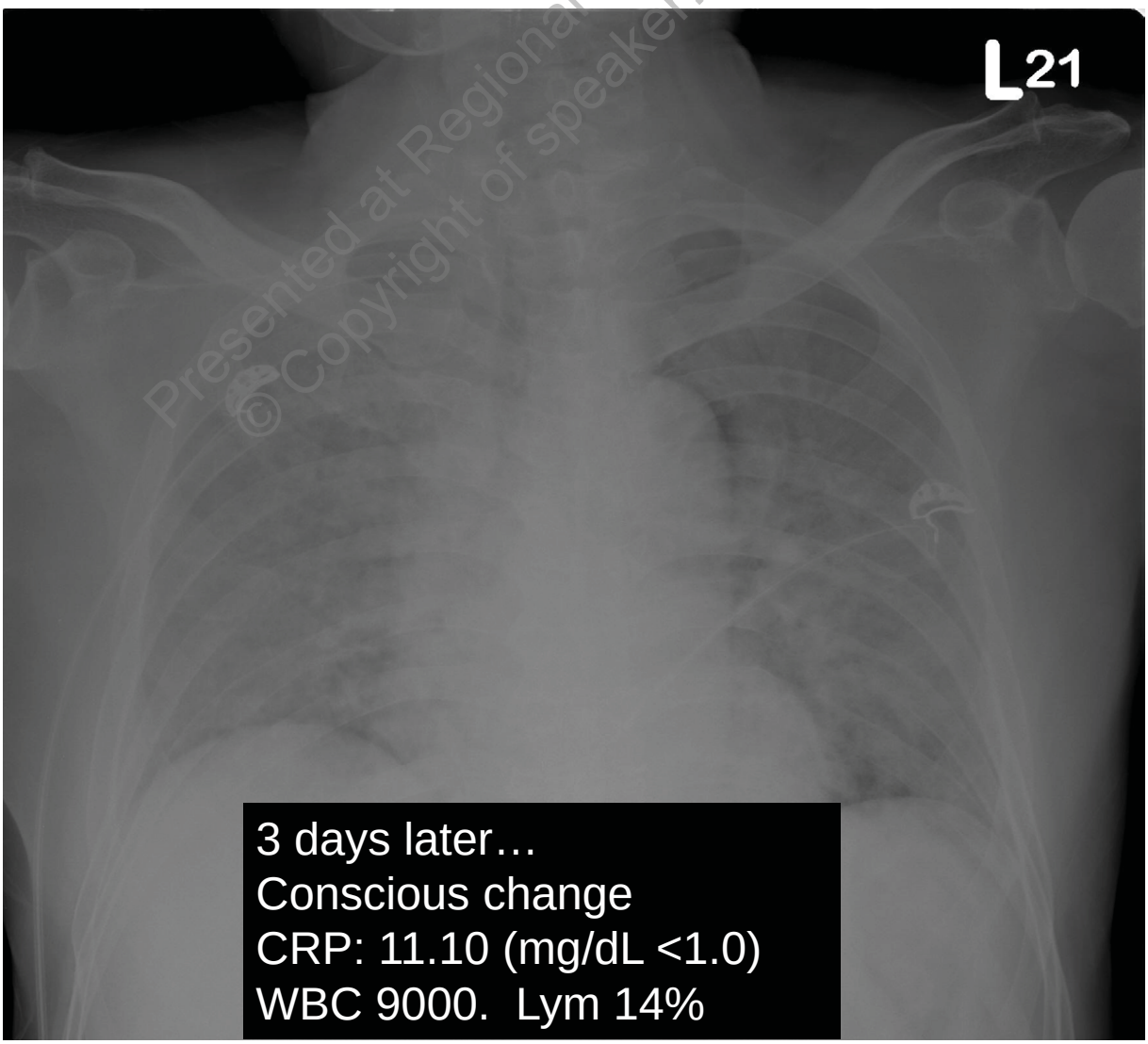
Pred. 20mg/day
AZA 100mg/day
HCQ 400mg/day

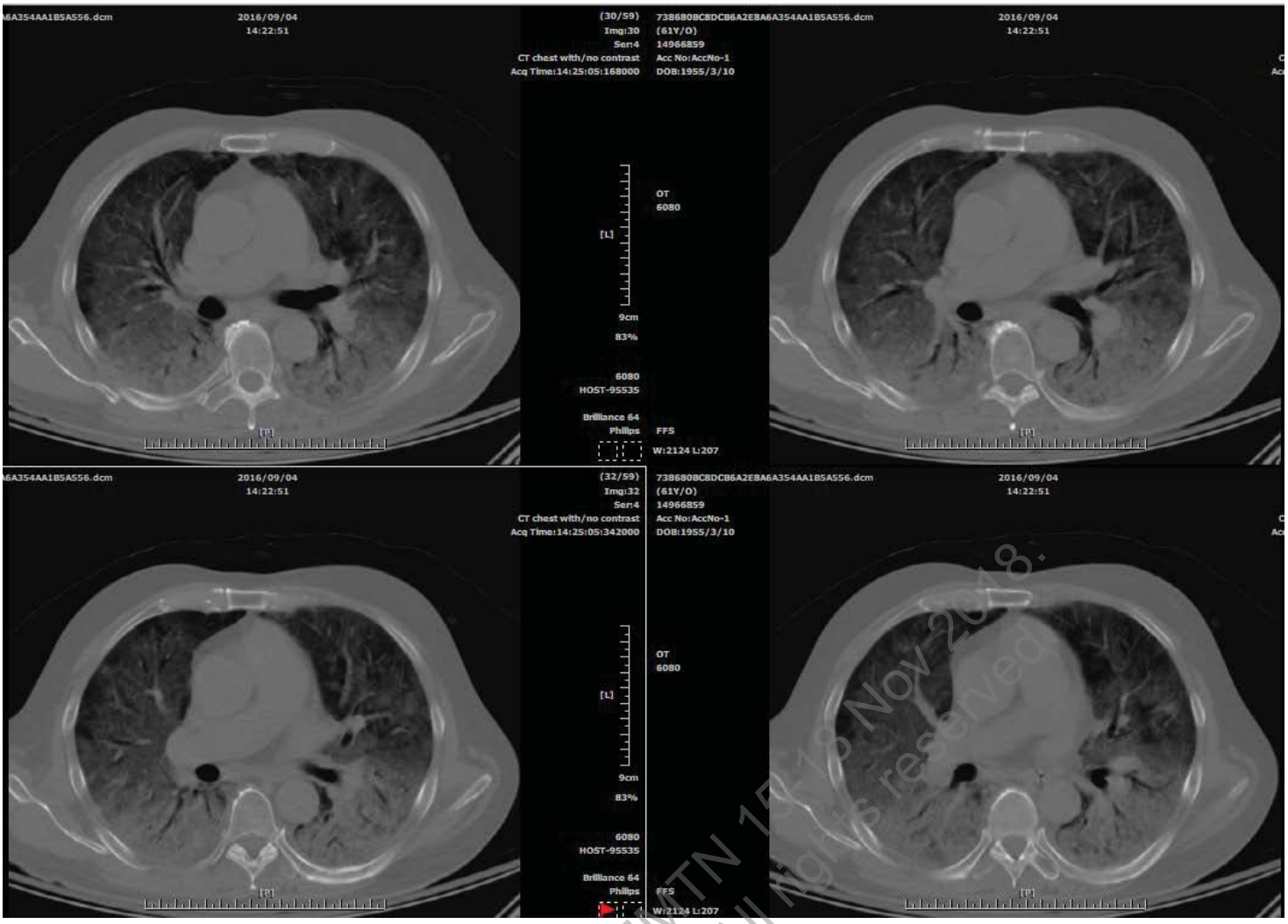
Abbreviations

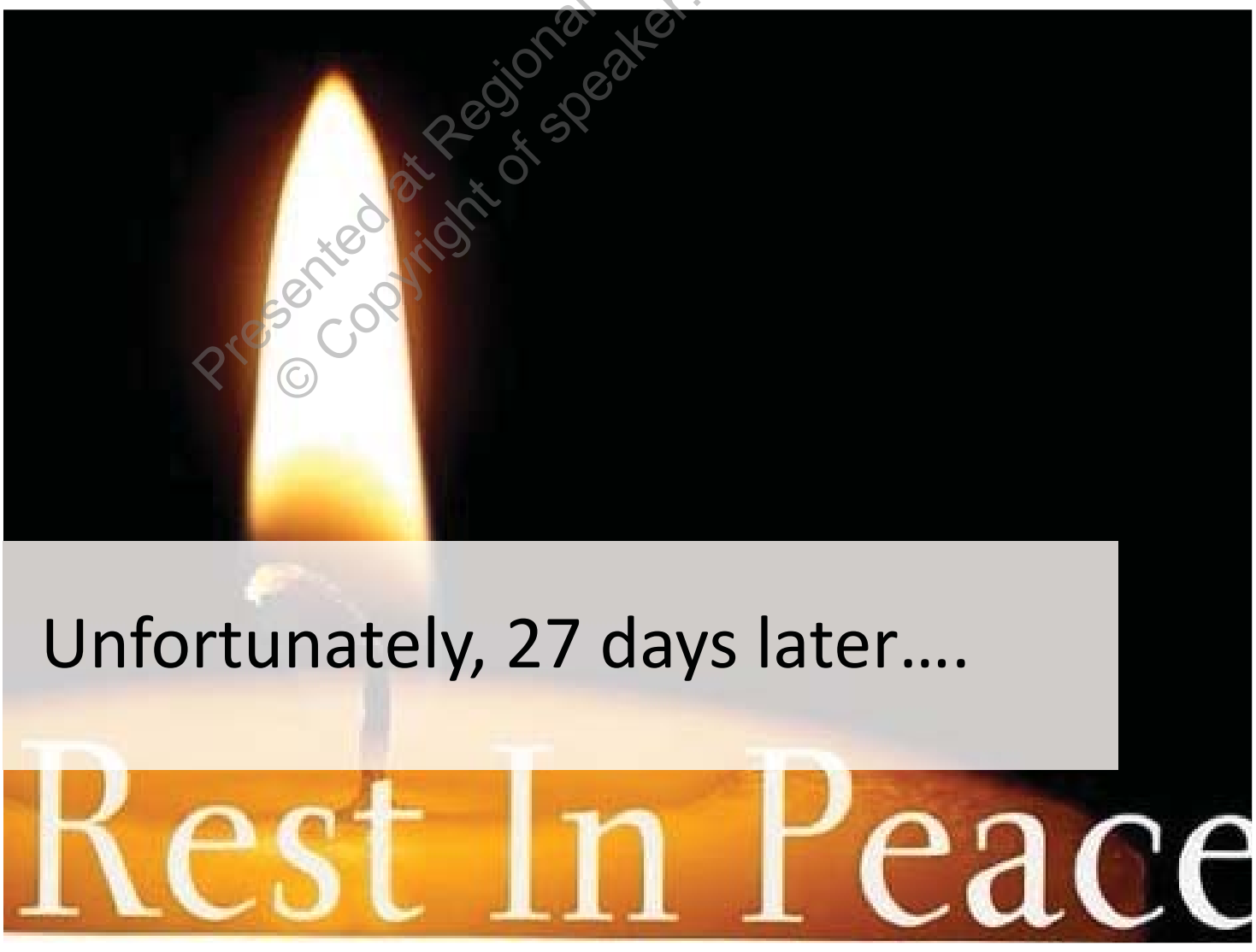
PV: pemphigus vulgaris
Pred. : Prednisolone
AZA : Azathioprine
HCQ : Hydroxychloroquine
MMF : Mycophenolate mofetil
RTX : Rituximab

One month after rituximab:
No new blisters for three weeks
Steroids was in tapering

- Post-herpetic neuralgia +++
- He felt too painful, thus he tried to cough to release the pain
- It was so painful, that continuous dry cough became severe for 3 days







PJP is an opportunistic infection related with low CD4 T cells.

Rituximab is targeting B cells, not T cells

Who should be blamed?

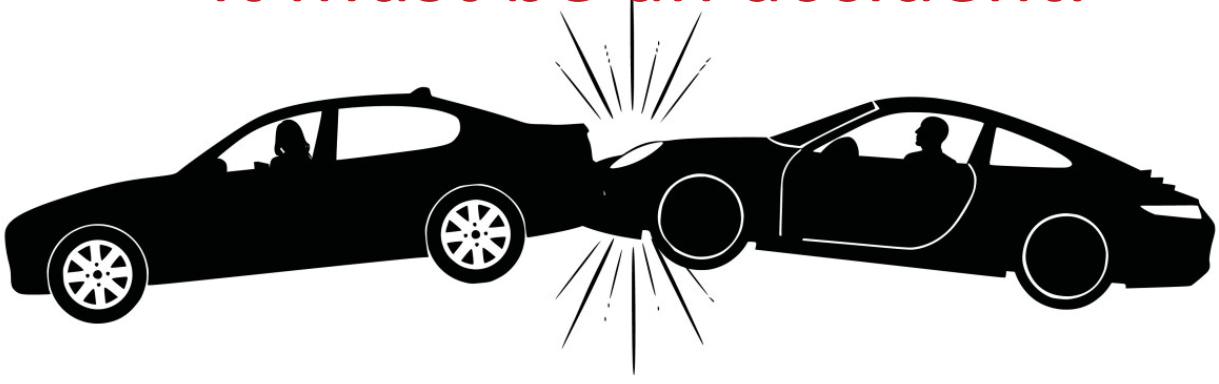
Corticosteroids

Mycophenolate
Azathioprine

PJP is an opportunistic infection related with low CD4- T cells.

Since rituximab is targeting B cells, not T cells…

It must be an accident.



JAMA Dermatology | Original Investigation

Determining the Incidence of *Pneumocystis* Pneumonia in Patients With Autoimmune Blistering Diseases Not Receiving Routine Prophylaxis

Kyle T. Amber, MD; Aniek Lamberts, MD; Farzan Solimani, MD; Arianna F. Agnoletti, MD; Dario Didona, MD; Ilona Euverman, HND; Emanuele Cozzani, MD, PhD; Lee Haur Yueh, MBBS, MRCP, MMed, FAMS; Giovanni Di Zenzo, PhD; Yael Anne Leshem, MD, MCR; Daniel Mimouni, MD; Michael Hertl, MD; Barbara Horvath, MD, PhD

IMPORTANCE *Pneumocystis* pneumonia (PCP) is a potentially lethal opportunistic infection that primary prophylaxis can help prevent. The risk of prophylactic therapy must be weighed against the incidence of PCP in the patient population. Prophylaxis most frequently involves trimethoprim-sulfamethoxazole, with second-line therapies, including atovaquone, dapsone, and pentamide. The indication for prophylaxis in immunocompromised patients without HIV is less well defined. Previously, an incidence of at least 3.5% has been proposed as a cutoff to justify prophylaxis.

OBJECTIVE To assess the incidence of PCP in patients with autoimmune blistering diseases receiving no routine prophylaxis.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective analysis of patient medical records to determine the incidence of PCP infections. The multicenter study was performed at tertiary care centers that provide care for patients with autoimmune blistering disease in Germany, Italy, Singapore, Israel, and the Netherlands. Patients had a confirmed diagnosis of pemphigus vulgaris/foliaceus, bullous pemphigoid, epidermolysis bullosa acquisita, mucous membrane pemphigoid/cicatricial pemphigoid, or anti-p200 pemphigoid.

MAIN OUTCOMES AND MEASURES To determine the incidence of PCP defined as patients with the *International Classification of Diseases, Ninth Revision (ICD-9)*, code 136.3, for PCP, or free text documentation of PCP occurring based on characteristic radiographic findings with elevated lactate dehydrogenase, or hospitalization for pneumonia with bronchioalveolar lavage demonstrating *Pneumocystis jiroveci* on confirmatory stains.

RESULTS A total of 801 patients with autoimmune blistering diseases were included in this study; their mean (SD) age was 66.5 (17.6) years, and a total of 465 (58%) were female. Only 1 patient developed PCP, resulting in an incidence rate of 0.1%. This incidence significantly fell below the recommended threshold of 3.5% (0.1% vs 3.5%, $\chi^2_1 = 27.0$; $P < .001$). This incidence was significantly lower than the previously reported incidence of PCP in all immunosuppressed dermatologic patients (0.1% vs 1.3%; $\chi^2_1 = 8.2$; $P = .004$).

Amber KT, et al. ***JAMA Dermatol***. 2017;153(11):1137-1141.

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- 1 of 801 (0.1%) autoimmune blistering disease patients developed Pneumocystis pneumonia
- 1 of 140 (0.7%) patients receiving rituximab

MAIN OUTCOMES AND MEASURES To determine the incidence of PCP defined as patients with the *International Classification of Diseases, Ninth Revision (ICD-9)*, code 136.3, for PCP, or free text documentation of PCP occurring based on characteristic radiographic findings with elevated lactate dehydrogenase, or hospitalization for pneumonia with bronchioalveolar lavage demonstrating *Pneumocystis jiroveci* on confirmatory stains.

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- Routine Pneumocystis Prophylaxis does NOT seem to be warranted.

membrane pemphigoid/cicatricial pemphigoid, or anti-p200 pemphigoid.

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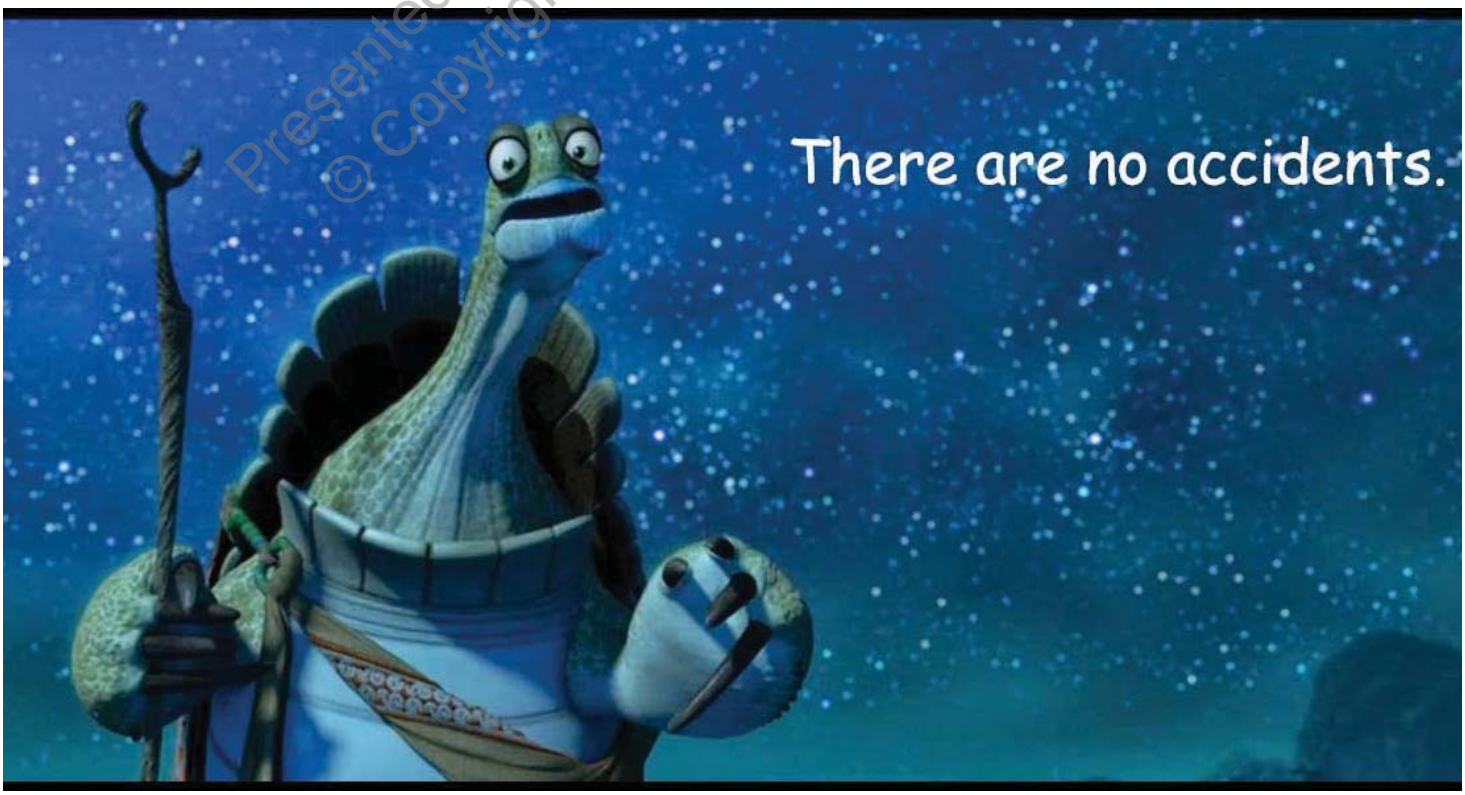
But, we found several similar cases, pemphigus with rituximab in the literature



Search PJP in pemphigus patients in Taiwan

National Health Insurance Research Database in Taiwan (2009.01~2013.12)

- Registry for catastrophic illness patients (HV) and the inpatient expenditures by admissions (DD) data
- PJP (ICD9 code: 136.3) in all patients diagnosed with pemphigus (ICD9 code: 694.4)

PJP in pemphigus patients in Taiwan during 2009~2013

391 new diagnosed pemphigus patients

52 of them received rituximab

- None of 339, who received conventional therapy had PJP
- 2 of 52 developed PJP (3.8%)

Wei, et al. ***Eur J Dermatol***. 2018 (Accepted)

during 2009 to 2013 in Taiwan
2 Severe PJP cases with intubation

Case 1: 58 year-old man

PJP attack

IV for 5 months RTX

Pred 40mg/day
AZA 100mg/day

Admission:
9 weeks

Case 2: 33 year-old man

PJP attack
23 weeks after last RTX

IV for 2 years RTX

Pred 30mg/day

3 weeks

It is only the beginning (Rituximab)

Date	
Aug, 2018	**Imbruvica (ibrutinib) Plus Rituximab for Waldenström's Macroglobulinemia**
Jun, 2018	**Pemphigus Vulgaris**
Apr, 2011	Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA)
Jan, 2011	**First-Line Maintenance Use in Follicular Lymphoma**
Feb, 2010	**Chronic Lymphocytic Leukemia**
Feb, 2006	**Moderate-to-Severe Rheumatoid Arthritis**
Feb, 2006	**Rituxan Plus CHOP or other Anthracycline-Based Chemotherapy Regimens for First-Line Treatment of Diffuse Large B-Cell Non-Hodgkin's Lymphoma**
Nov, 1997	Non-Hodgkin's Lymphoma

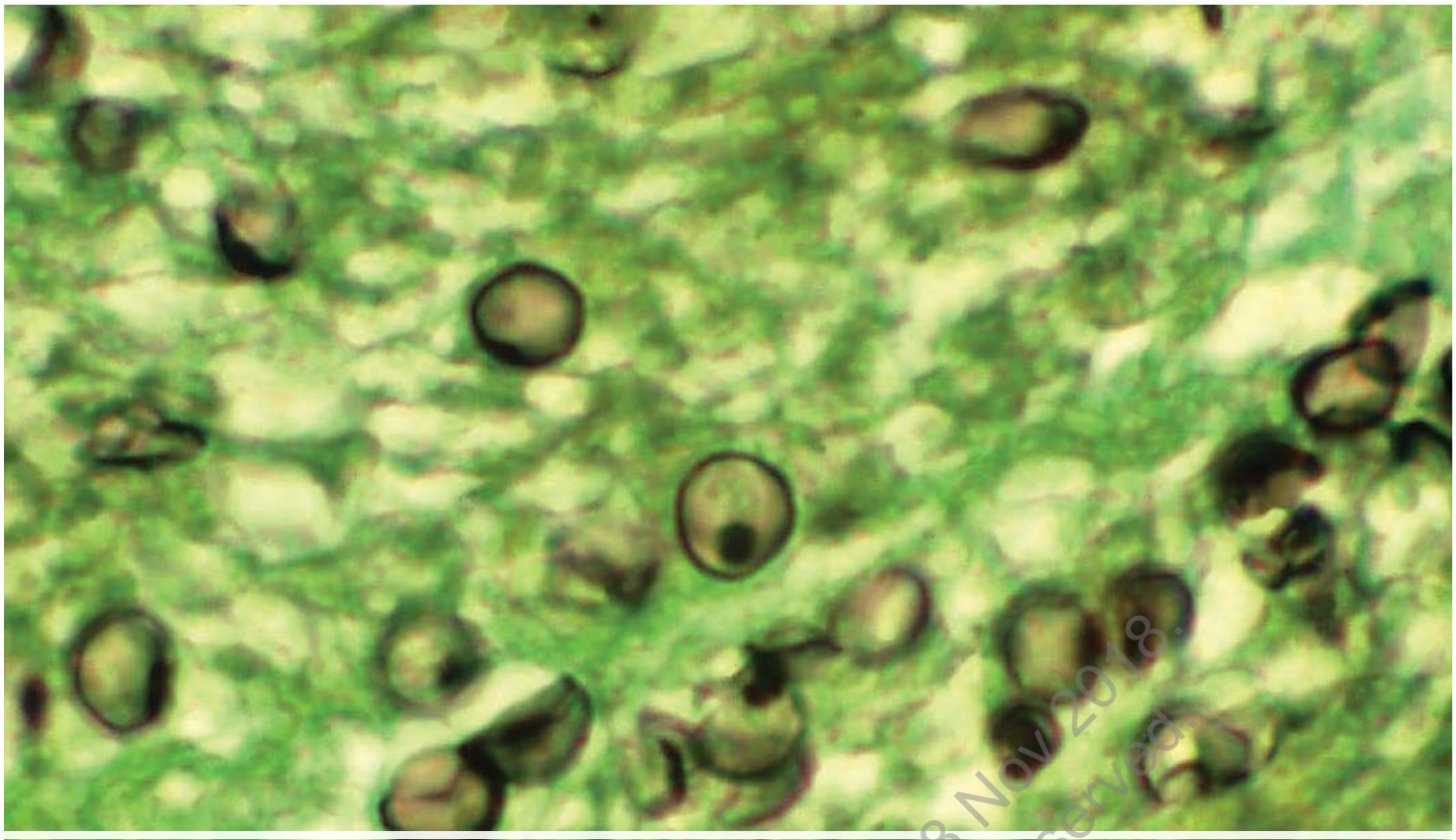
Outlines

01 Case sharing

02 *Pneumocystis jiroveci (PJP)*

03 HIV vs. non-HIV

04 Prophylaxis



General of *Pneumocystis jiroveci*

Pneumocystis jiroveci
(Pneumocystis carinii)

1909: Carlos Chagas found cystic forms (lung of guinea pigs)

1910 : Antonio Carini identified it as protozoa (lung of rats)

1952: Otto Jirovec found in human

- 1909：Carlos Chagas found cystic forms (lung of guinea pigs)
- 1910 : Antonio Carini (lung of rats)
- 1952: Otto Jirovec found in human

- 1976 : opportunistic infection in children (congenital T cell immunodeficiency & hematological malignancies)

Walzer, Peter D., et al. "Pneumocystis carinii pneumonia and primary immune deficiency diseases." *National Cancer Institute monograph* 43 (1976): 65-74.

- *Pneumocystis* has been found in the lungs of rats, rabbits, mice, dogs, sheep, goats, ferrets, chimpanzees, guinea pigs, horses, and monkeys.

- Protozoan?
  (DNA/RNA/ genomic study) --> fungus!

- Lack of ergosterol
- Can not grow in culture --> difficult to study

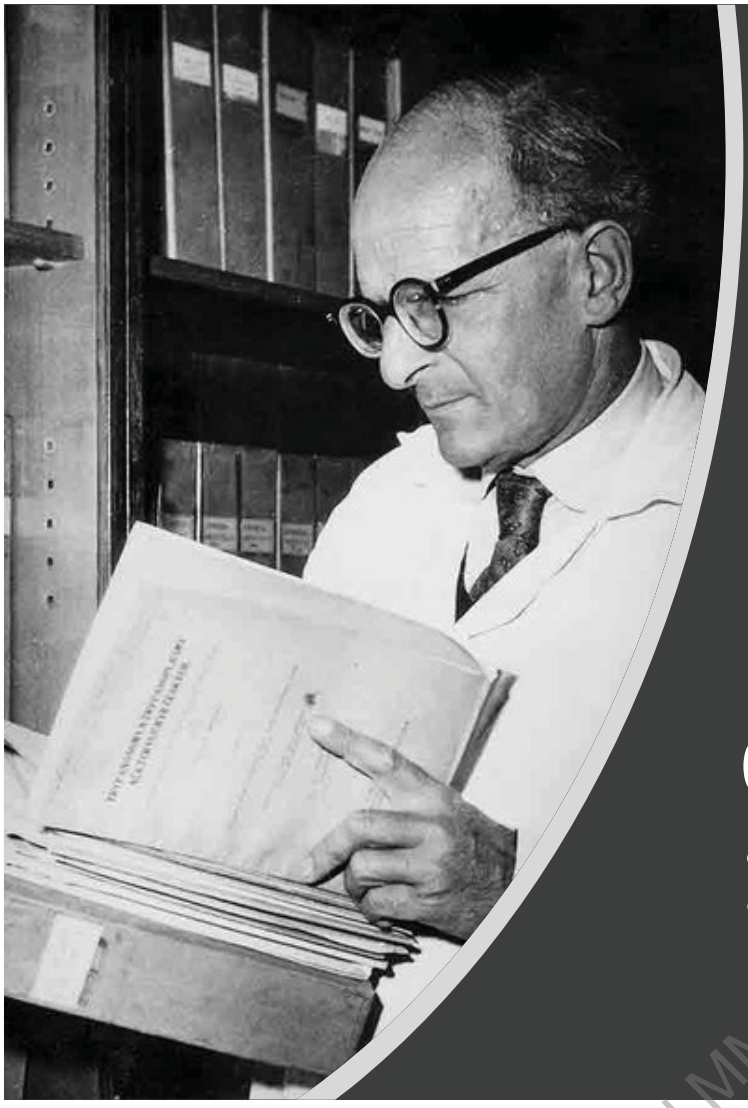
- Five species-specific *Pneumocystis* species have been identified:
  - *Pneumocystis carinii*
    Pneumocystis wakefieldiae in rats
  - *Pneumocystis murina* in mice
  - *Pneumocystis oryctolagi* in rabbits
  - *Pneumocystis jiroveci* in humans

DNA analyses reveal:

Pneumocystis species infecting lungs of various mammalian species are quite different and their infection is host specific.

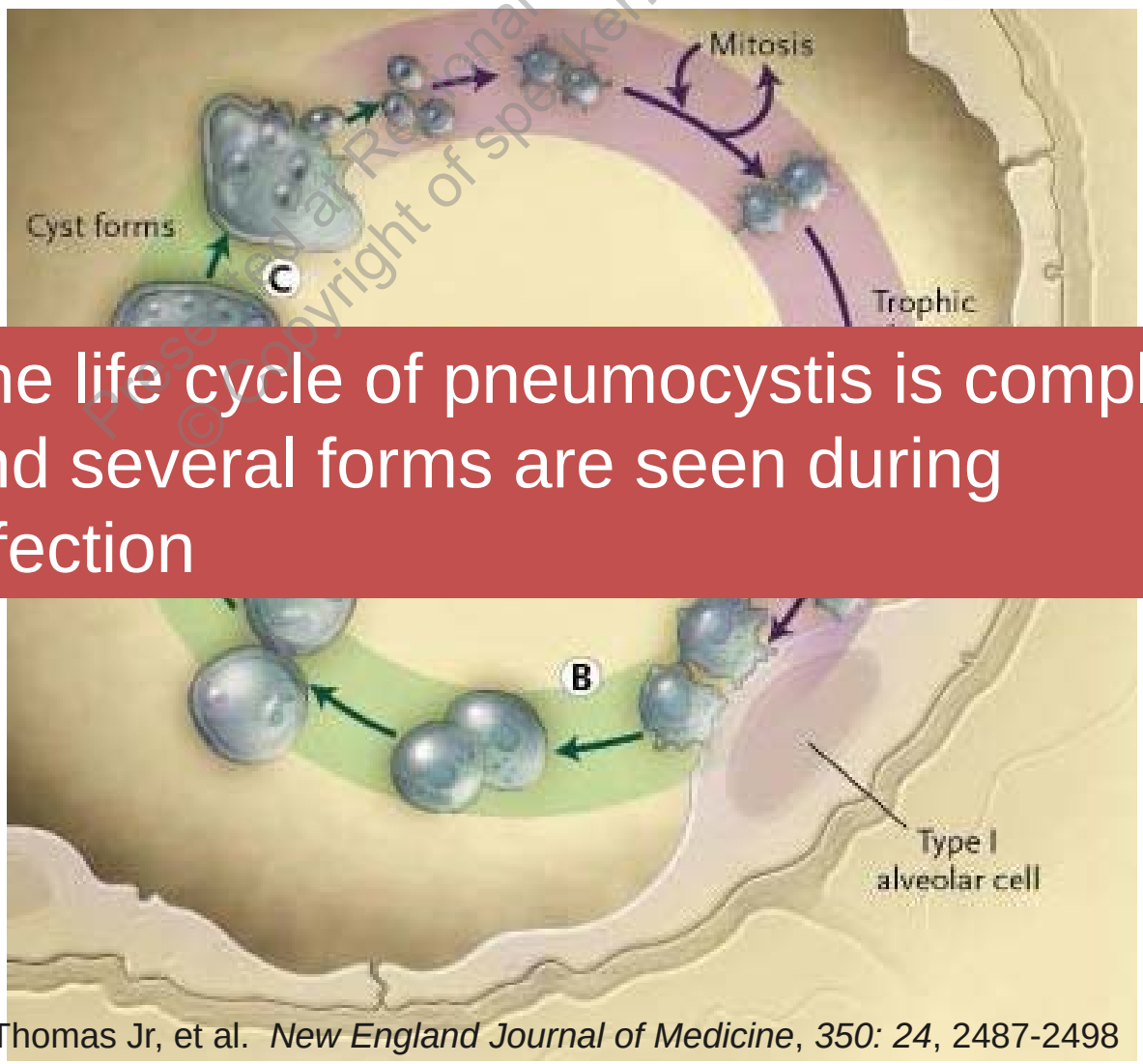
Aliouat EM, et al. J Eukaryot Microbiol. 1994 Sep-Oct; 41(5):71S.

Sokulska M, et al Parasitol Res. 2015 Oct;114(10):3577-85.



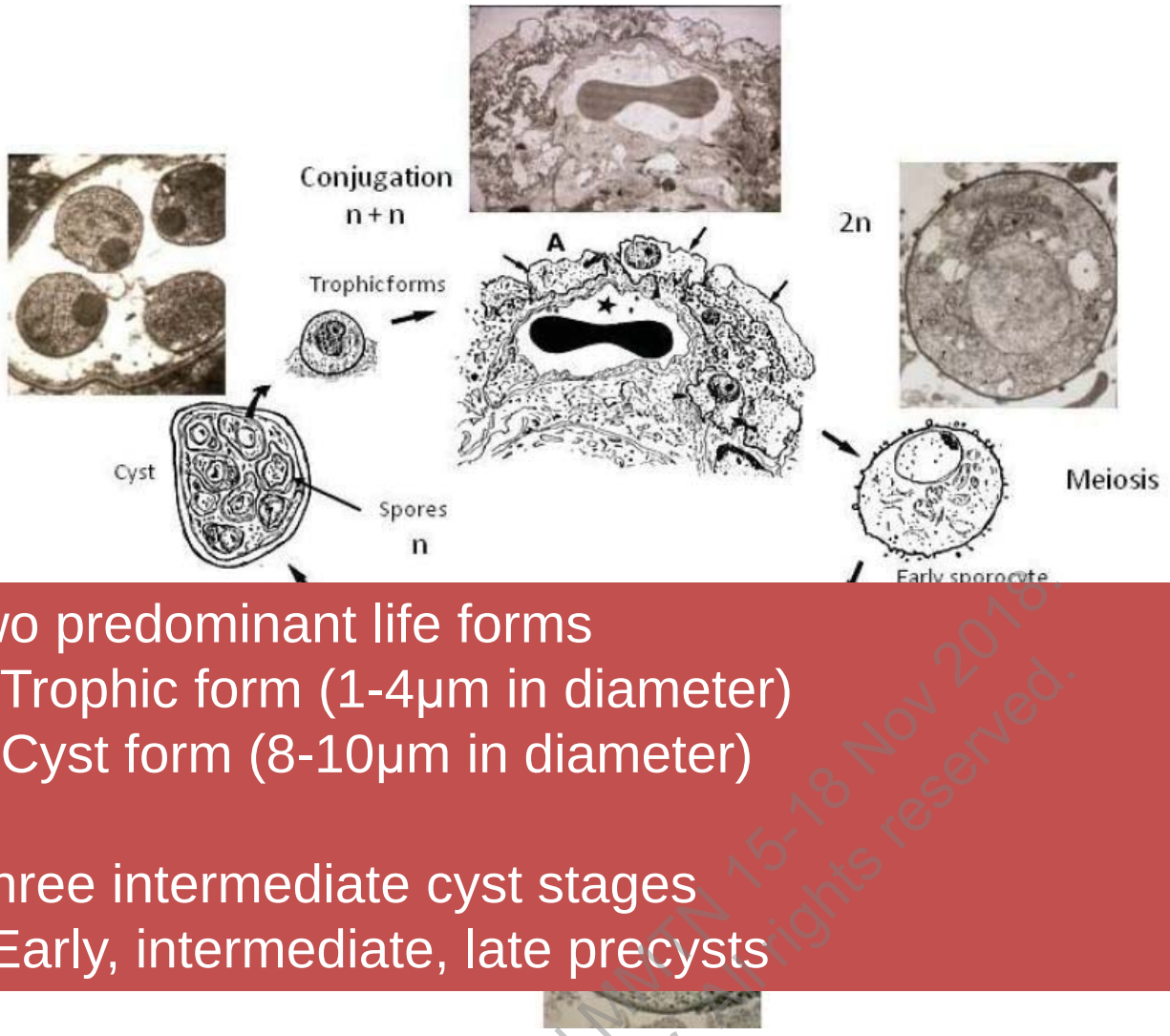
In 1999, the human variant of *Pneumocystis carinii* was renamed *Pneumocystis jiroveci*

Otto Jírovec
1907 – 1972



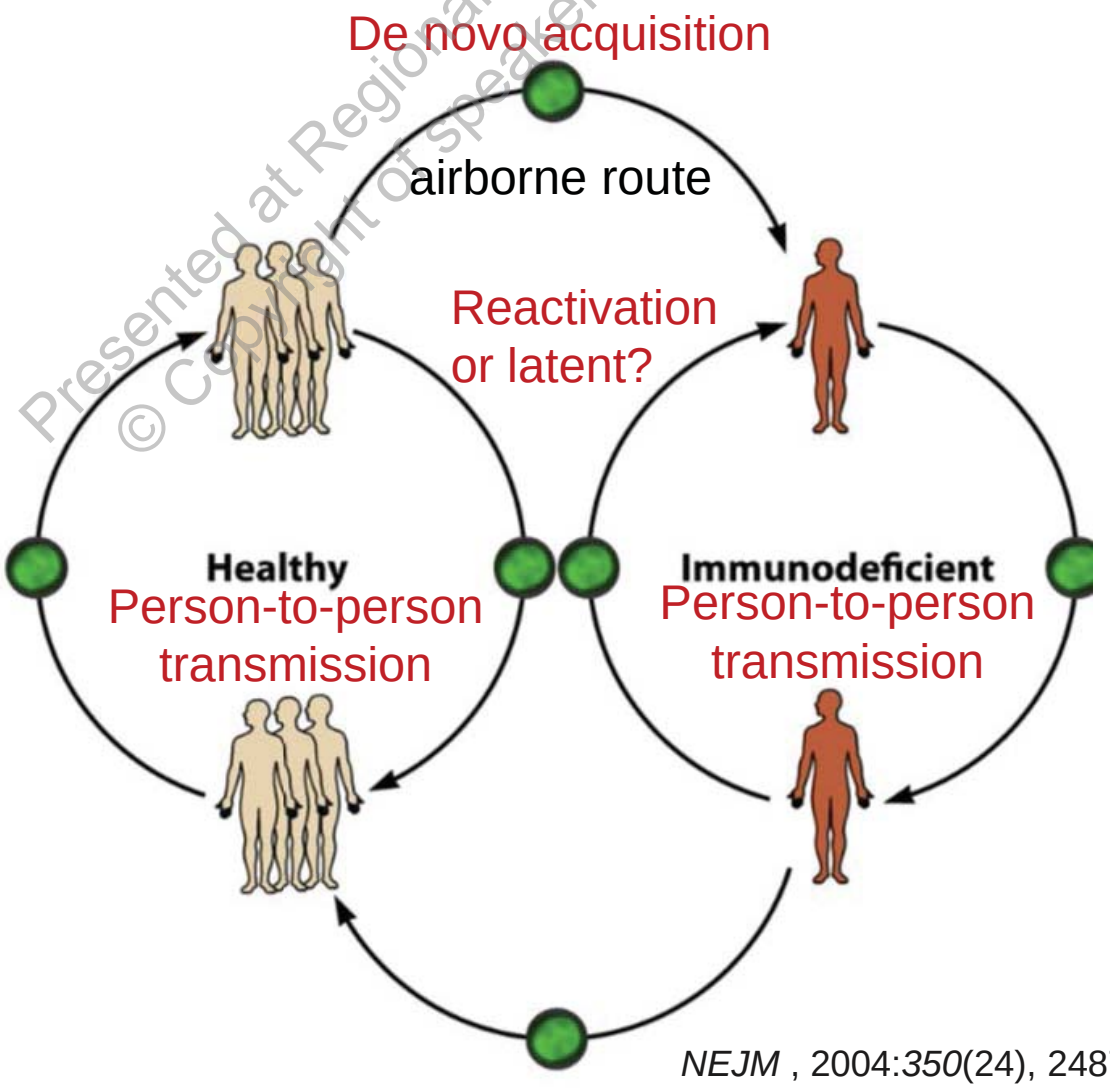
The life cycle of pneumocystis is complex, and several forms are seen during infection

Thomas Jr, et al. *New England Journal of Medicine*, *350: 24*, 2487-2498



Two predominant life forms
- Trophic form (1-4μm in diameter)
- Cyst form (8-10μm in diameter)

Three intermediate cyst stages
- Early, intermediate, late precysts



NEJM , 2004:*350*(24), 2487-2498.

Pathophysiology

- PJP occurs when both cellular immunity and humoral immunity are defective.

- Activated alveolar macrophages without CD4-positive cells are unable to eradicate *Pneumocystis* organisms.

- Impaired immunity, especially those with CD4+ T cell count below 200/µl

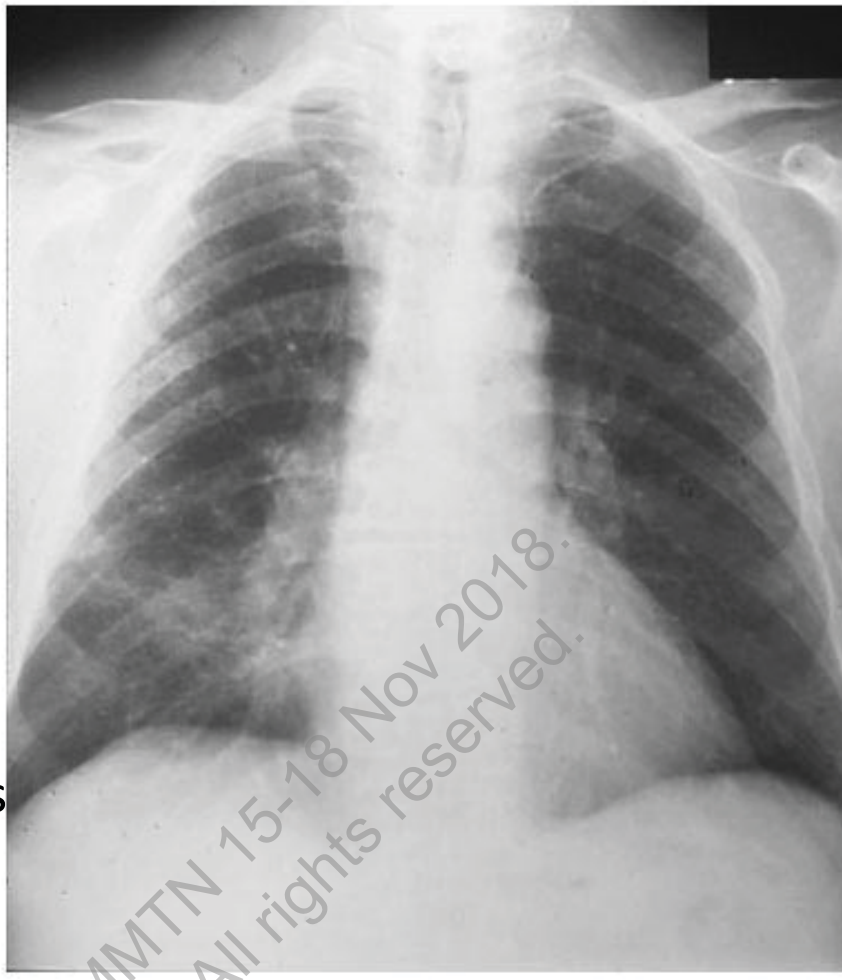
- Before widespread use of PJP prophylaxis and effective ART, PJP seen in 70-80% of AIDS patients in U.S.A.

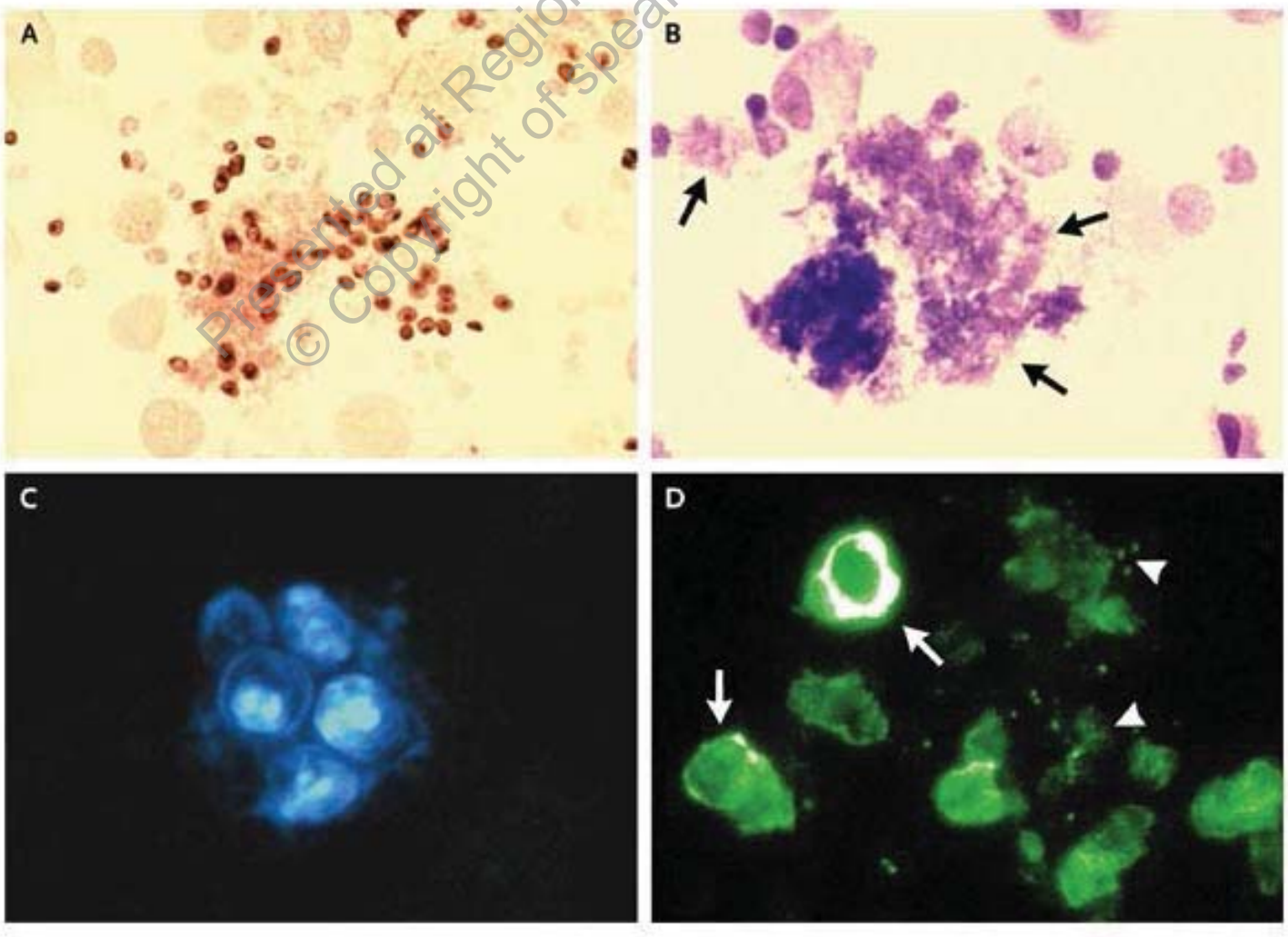
N Engl J Med. 1990 Jan 18; 322(3):161-5.

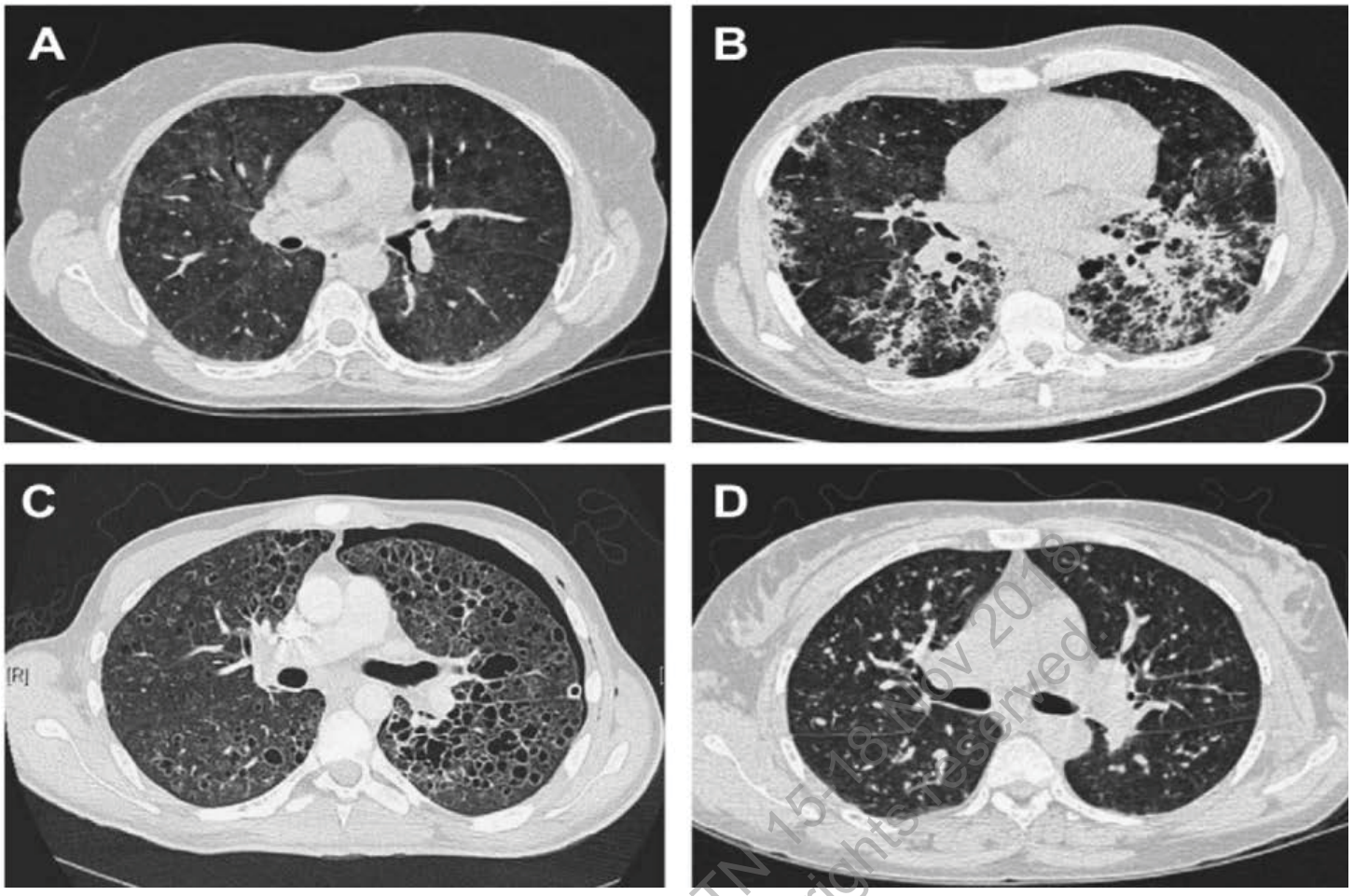
Clinical presentation
Nonspecific

Progressive exertional dyspnea, fever, nonproductive cough, chest discomfort

CXR:
¼: normal
Most: interstitial infiltrates

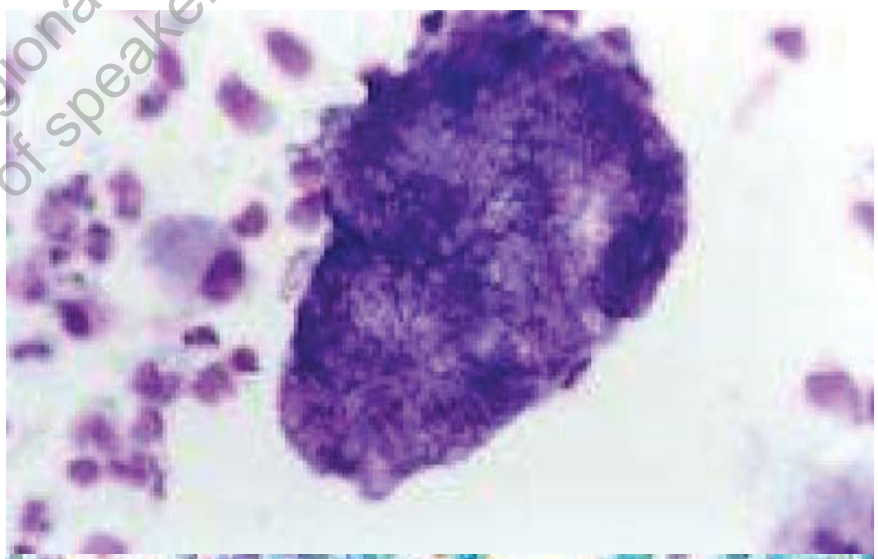




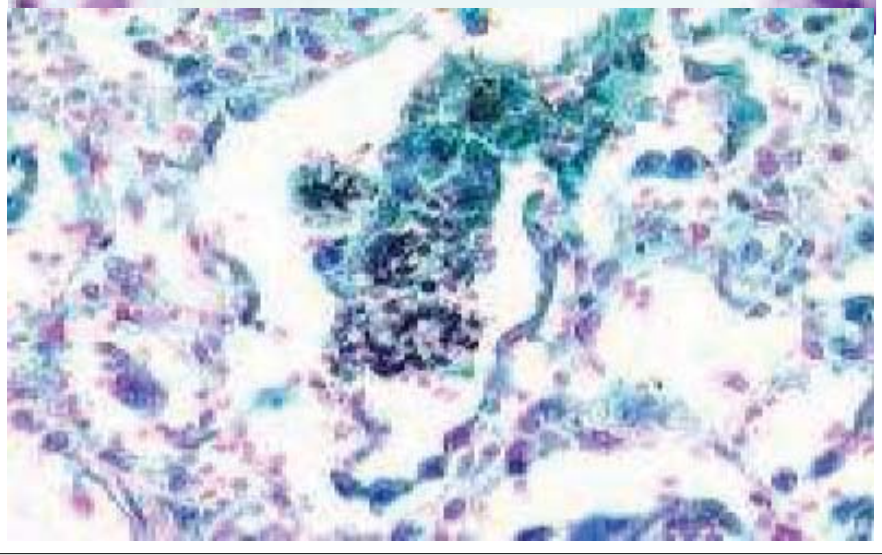


Histology

- In the past, histopathology is necessary for a definitive diagnosis.



- Now: quantitative PCR for sputum or induced BAL



PJP Prophylaxis

- Trimethoprim- sulfamethoxazole (TMP-SMX):
  160/800 mg, three times/week (2 tablets)
  or 80/400 mg, one time/day (1 tablet)

- Prophylaxis is highly effective and successful in HIV-positive patients

PJP is no longer a serious issue for HIV patients

CD4 cells less than 200/µl is strongly associated with PJP

- a useful threshold to commence prophylaxis

Outlines

01 Case sharing

02 *Pneumocystis jirovecii*

03 PJP in HIV-uninfected group

04 Prophylaxis

PJP with HIV vs. non-HIV

	HIV positive	HIV negative
Onset	Gradual	Abrupt
Progression to respiratory failure	2 weeks to 2 months	Less than one week
Severity of respiratory insufficiency	+	++
Delayed in diagnosis		common
Organism load	++ (larger)	+ (smaller)
Mortality	Less than 10%	30 - 60%

J Microbiol Immunol Infect. 2014 Feb; 47(1):42-7.

Variables	Odds Ratio (95% confidence interval)	*p* value	Score points
Age		<0.0001	

Main risk of intubation and mortality: Delay in giving proper antibiotics (within 3 days onset of respiratory symptoms)

Days between respiratory symptom onset and ICU admission		<0.0001	
<3 days	/		**0**
3 to 5 days	4.35 (2.53-7.49)		**+3**
>5 days	4.98 (3.12-7.92)		**+3**
Shock at ICU admission	0.47 (0.29-0.75)	<0.0001	**-1.5**
Chest X-ray: not alveolar	3.31 (1.55-7.06)	<0.0001	**+2.5**

A Multivariable Prediction Model for Pneumocystis jirovecii Pneumonia in Hematology Patients with Acute Respiratory Failure. ***Am J Respir Crit Care*** 2018

Detection of *P. jiroveci* and PJP diagnosis is more difficult in HIV-negative patients

- The rapid diagnosis of PJP is crucial to reduce mortality and morbidity.

- Low fungal burden in HIV-negative patient.

Emerg Infect Dis. 2014 Sep; 20(9):1490-7.

Can we predict who is in higher risk of PJP (in HIV-negative group)?

Non-HIV with PJP (specific diseases)

- 116 non-HIV patients between 1985 and 1991
  - Hematologic malignancies (30.2%)
  - Organ transplantation (25.0%)
  - Inflammatory disorders (22.4%)
  - Solid tumors (12.9%)
  - Miscellaneous conditions (9.5%)

Yale SH, Limper AH. *Pneumocystis carinii pneumonia* in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. ***Mayo Clin Proc*** 1996; 71: 5-13.

Non-HIV with PJP (specific agents)

- systemic corticosteroids
(>20 mg of Prednisone for greater > 8 weeks)

- cytotoxic chemotherapies (e.g. fludarabine or cyclophosphamide)

- Specific biological agents : Alemtuzumab
Deplete T cells, such as anti-CD52 monoclonal Ab

PJP in HIV-uninfected patients with Rituximab

30 patients

3 patients received rituximab without steroids or cytotoxic agents

Mayo Clinic in Minnesota, from 1998 to 2011

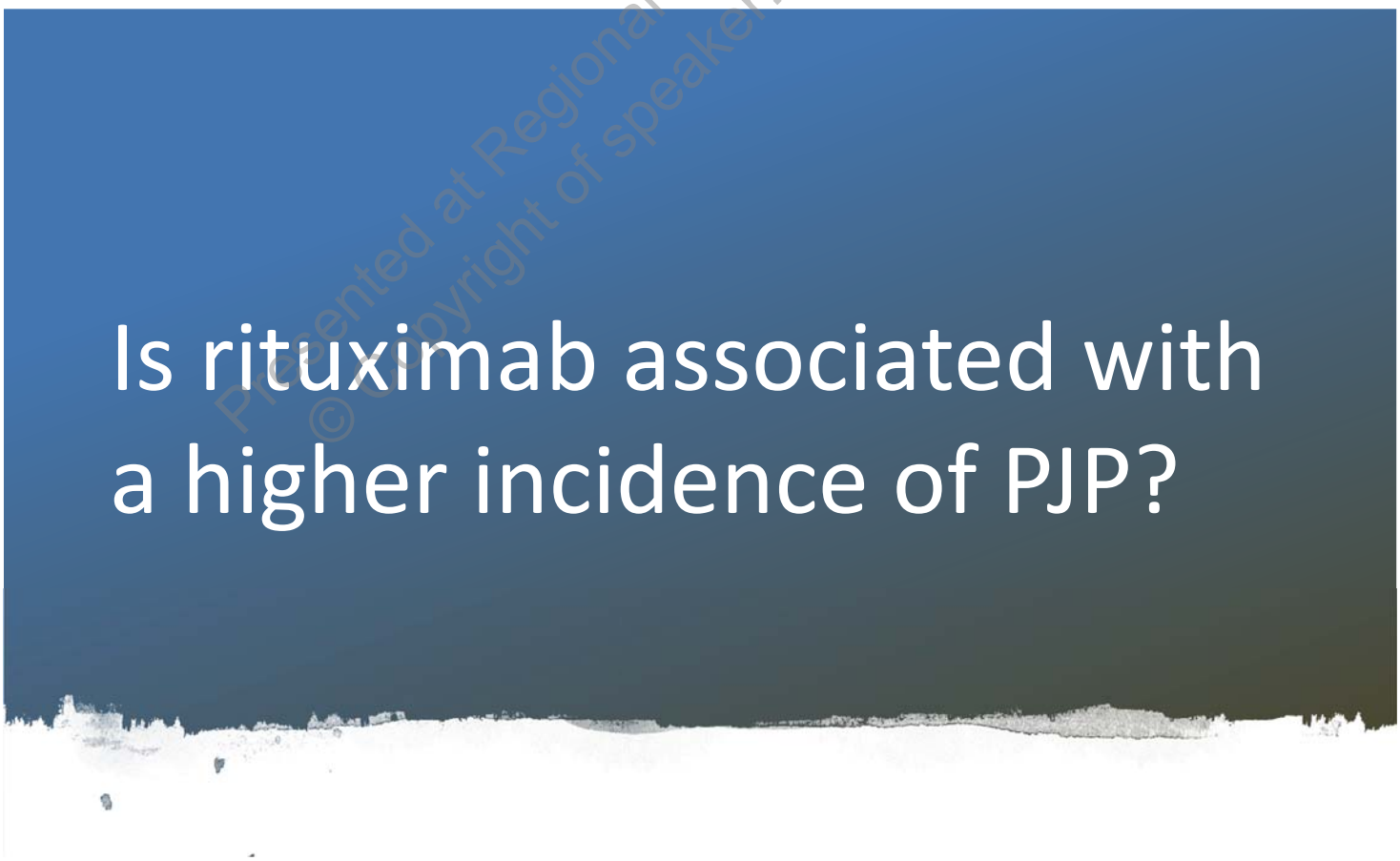
Martin-Garrido et al. ***Pneumocystis* pneumonia in patients treated with rituximab**. ***Chest***, 144 (1) (2013), pp. 258-265

PJP in HIV-uninfected patients with Rituximab (non-malignancies)

- 11 non-HIV patients:
  - 3 autoimmune haemolytic anemia
  - 3 ANCA(+) vasculitis
  - 2 acquired haemophilia
  - 2 pemphigus
  - 1 dermatomyositis

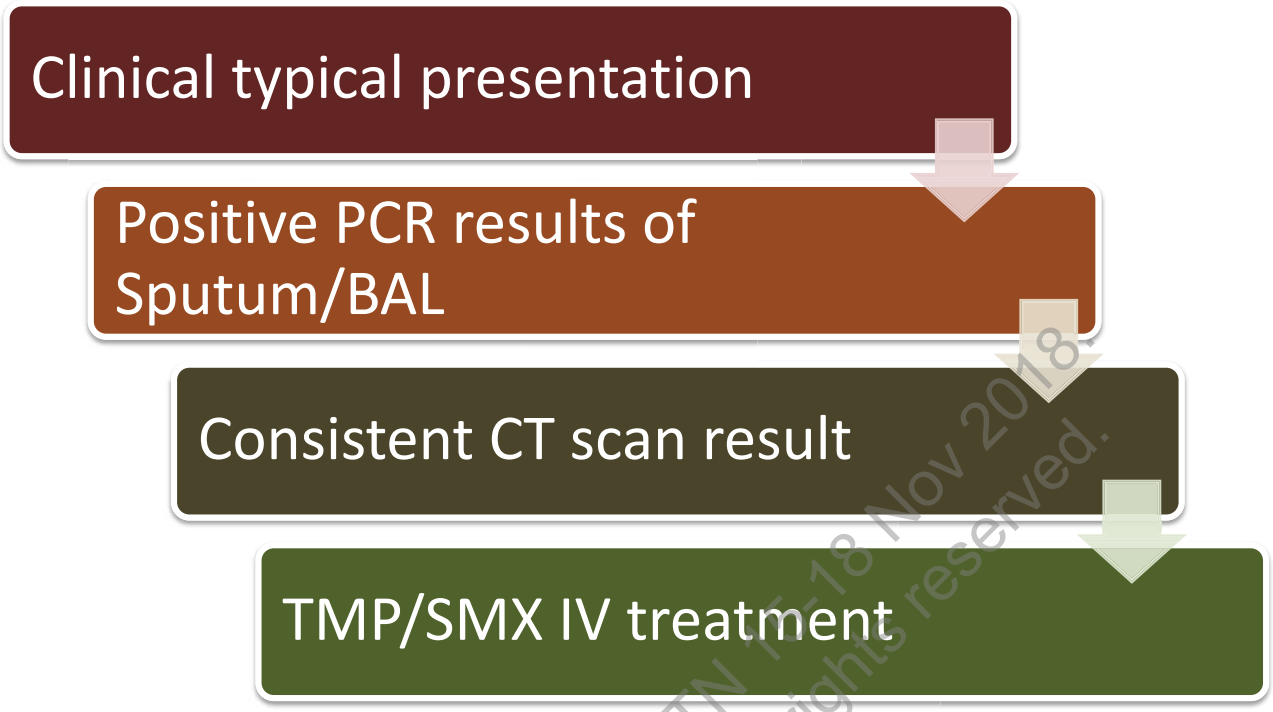
- overall mortality rate was 27%

Alexandre, K., et al. "*Pneumocystis jiroveci* pneumonia in patients treated with rituximab for systemic diseases: Report of 11 cases and review of the literature." ***European journal of internal medicine*** 50 (2018): e23-e24.



PJP infection (Algorithm of confirming cases)

2014.05~2016.09 in Kaohsiung Veterans General Hospital



Disease group of PJP	N= 44
HIV/AIDS without lymphoma	22 (50%)
HIV/AIDS with DLBCL &rituximab	2 (4.5%)
Non-HIV with rituximab	5 (11.4%)
Others without rituximab	15 (34.1%)
Total	44 (100%)

During 2014.05~2016.09 in VGHKS, PJP infection were diagnosed in 44 patients.

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HIV/AIDS without lymphoma	22 (50%)
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Non-HIV with rituximab	5 (11.4%)
Others without rituximab	15 (34.1%)
Total	44 (100%)

During 2014.05~2016.09 in VGHKS, PJP infection were diagnosed in 44 patients.

- HIV (-) & Rituximab (+) : 5 cases
  - Idiopathic thrombocytopenic purpura: (1)
  - Pemphigus vulgaris: (1)
  - Lymphoma: (3)

B cell lymphoma, HIV-negative, without hematopoietic transplant patients, treated with rituximab-based therapy in Kaohsiung Veterans General Hospital in Taiwan
2014.05~2016.09

Type*	Number	PJP
Diffuse large B cell lymphoma	87	2
Follicular lymphoma	9	1
Others **	7	0
Total	103	**3 (2.91%)**

Outlines

01 Case sharing

02 *Pneumocystis jiroveci*

03 HIV vs. non-HIV

04 Prophylaxis

Is PJP prophylaxis effective for HIV-negative patients?

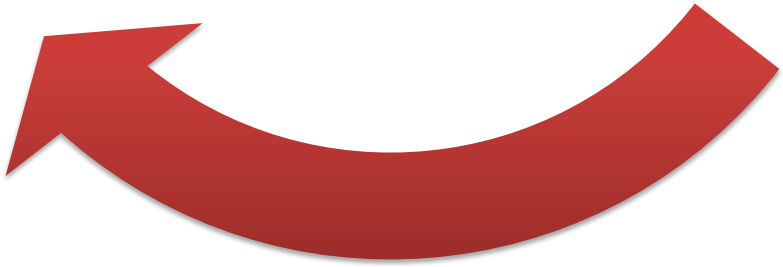
Definitely yes!

Green H,et al.Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. ***Mayo Clin Proc***. 2007. September; 82(9):1052–9. .

(literature & our studies)

PJP is not rare (3%)

Prophylaxis is effective



PJP: 3%

Prophylaxis is effective

No need for prophylaxis!

Why?

Some specialists tell us not to do prophylaxis, because …

- 1. PJP prophylaxis is not safe
- 2. True incidence of PJP is low (your studied sample size is too small)

A systematic review and meta-analysis of randomized controlled trials (ALL)recommended PcP prophylaxis in HIV-uninfected patients

when the risk for PJP is >3.5%.

Prophylaxis of *Pneumocystis* pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials
Mayo Clin Proc, 82 (9) (2007), pp. 1052-1059

Based on this assertion, most of aforementioned diseases do not need prophylaxis

Event rate (%)	NNT	Clinical conditions among immunocompromised HIV-uninfected patients
10	11	Allogeneic bone marrow transplant, acute lymphoblastic leukemia, solid organ transplant, severe combined immunodeficiency syndrome
3.5	32	Wegener granulomatosis, rhabdomyosarcoma
1.5	73	Non-Hodgkin disease, central nervous system tumors, polymyositis/dermatomyositis
1	110	Systemic lupus erythematosus, polyarteritis nodosa, scleroderma, Pemphigus, long-term corticosteroid
0. 1	1099	Rheumatoid arthritis

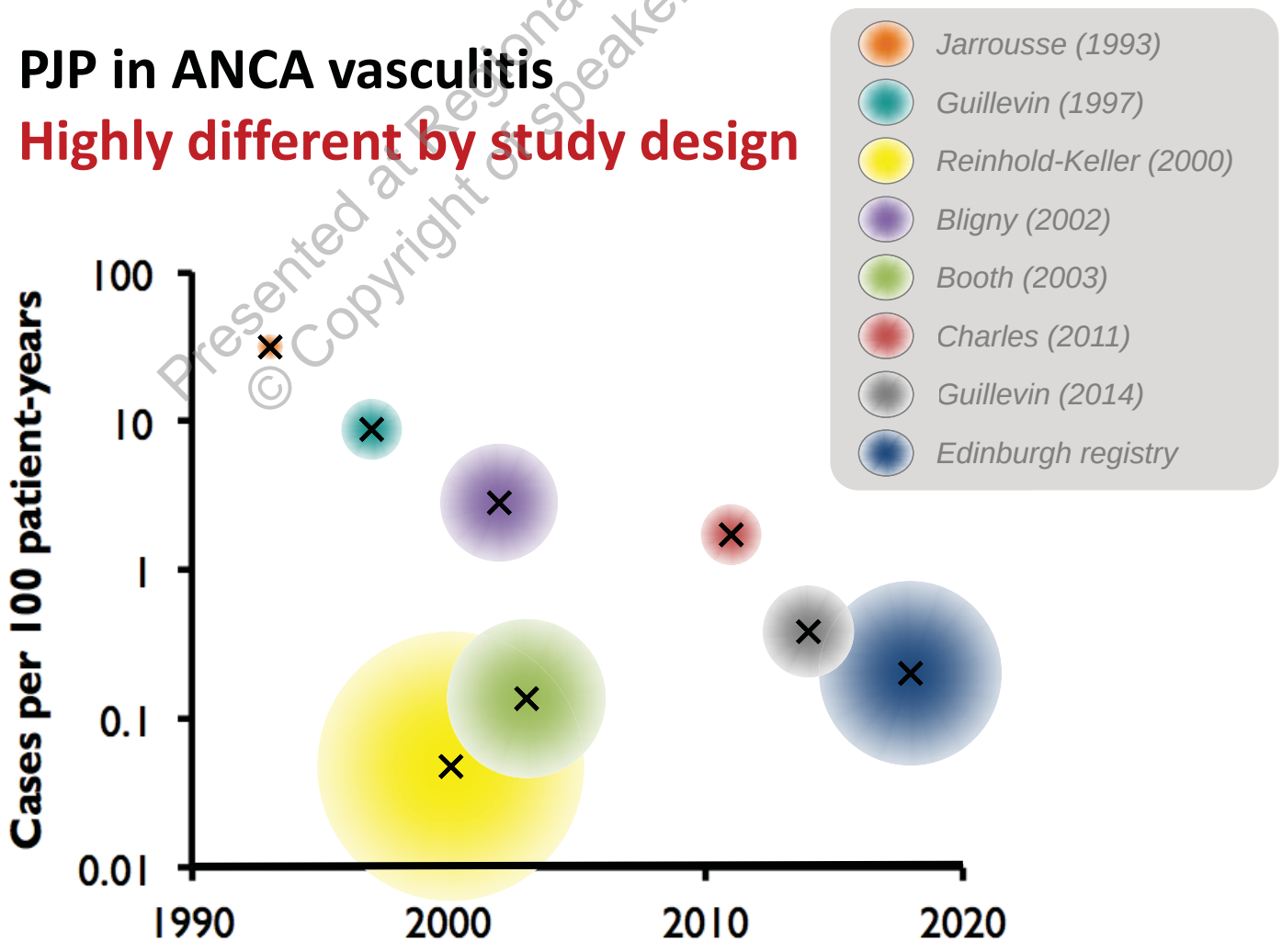
Rodriguez M, and Fishman JA: Prevention of infection due to . ***Clin Microbiol Rev*** *2004*; 17: pp. 770-782

If the reported incidences of PJP are not correct…

Incidence (%)	Disease types in non–HIV-infected patients
10	Allogeneic bone marrow transplant, acute lymphoblastic leukemia, solid organ transplant, severe combined immunodeficiency syndrome
3.5	Wegener granulomatosis (ANCA vasculitis)
1.5	Hodgkin disease, central nervous system tumors, polymyositis/dermatomyositis
1	Systemic lupus erythematosus, polyarteritis nodosa, scleroderma, pemphigus, pemphigoid, other long-term corticosteroid treatment
0.1	Rheumatoid arthritis

PJP in ANCA vasculitis

Highly different by study design



https://www.google.com.tw/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwiXkJaH4NPeAhUCE7wKHV9ADOgQFjAAegQICRAC&url=http

PJP in Hon-Hodgkin's lymphoma treated with rituximab

Reported PJP infection rate: 1.7 % ~ 14%

Author (ref)	Year	Pts. n.	Incidence (%)
Kim (12)	2013	713	2.0-4.5
Kurokawa (13)	2010	114	1.7-4.4
Kamel (14)	2010	47	4.3-10.6
Hashimoto (2)	2010	176	3.4
Katusya (15)	2009	129	3.2
Venhuizen (16)	2008	30	10
Kolstad (10)	2007	46	14

Leukemia & Lymphoma 2010; **51**:797–801

We are questioning the concept –
3.5% as a threshold for PJP prophylaxis
in HIV-negative patients.

True incidence?

Impact of PJP ?

Benefits of prophylaxis outweigh adverse effect?

It is very difficult to answer these questions by a single center or a group.

True incidence?

Impact of PJP ?

Benefits of prophylaxis outweigh adverse effect?

A hospital based study:

Advantage:

Solid evidences for diagnosis of PJP

Limitation:

Sample size is small.

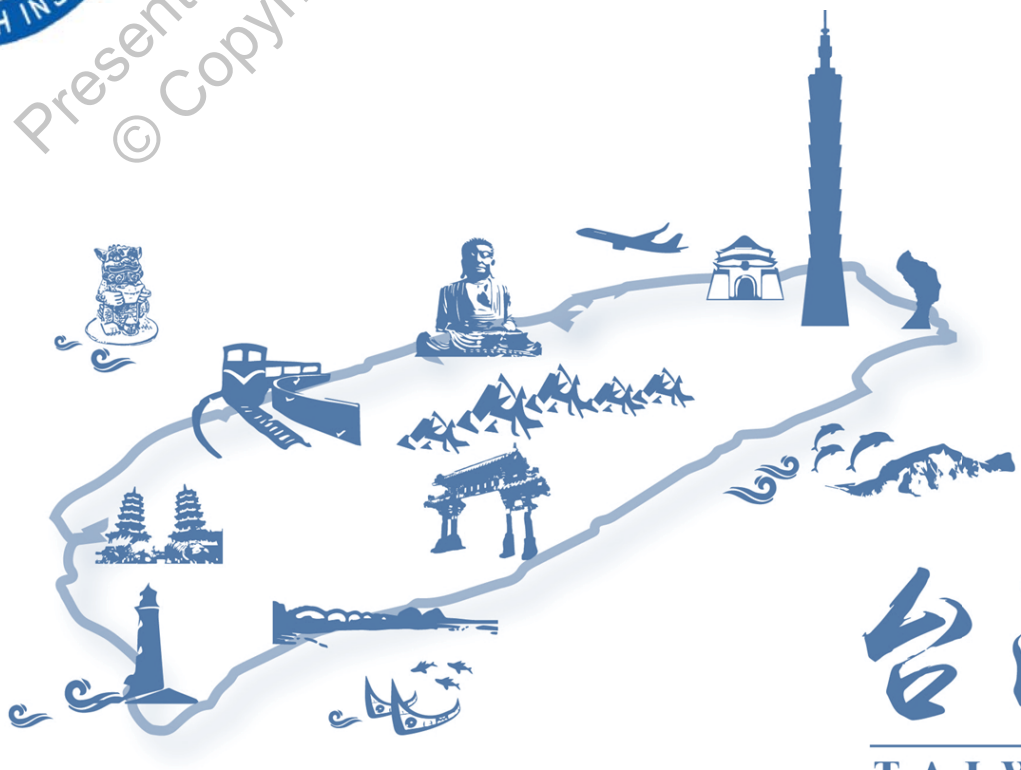
High diversity in clinical characters and treatment regimens.

Even in a giant center or an alliance

- During this time frame, a significant number of patients may receive rituximab at outside institutions either before or after care at the studied centers.

- No data of the entire population.

全民健康保險研究資料庫
National Health Insurance Research Database



全民健康保險研究資料庫
National Health Insurance Research Database

Taiwan National Health Insurance (NHI) has been 23 years since its historical inauguration in 1995.

NHI cover 99.9% of Taiwan population, with universal health coverage to Taiwan's population of 23.5 million.

HV database & National Health Insurance Database 2006/01~2013/12

Newly diagnosed HIV uninfected, Non-Hodgkin lymphoma (ICD 9: 200, 202): n= 20961

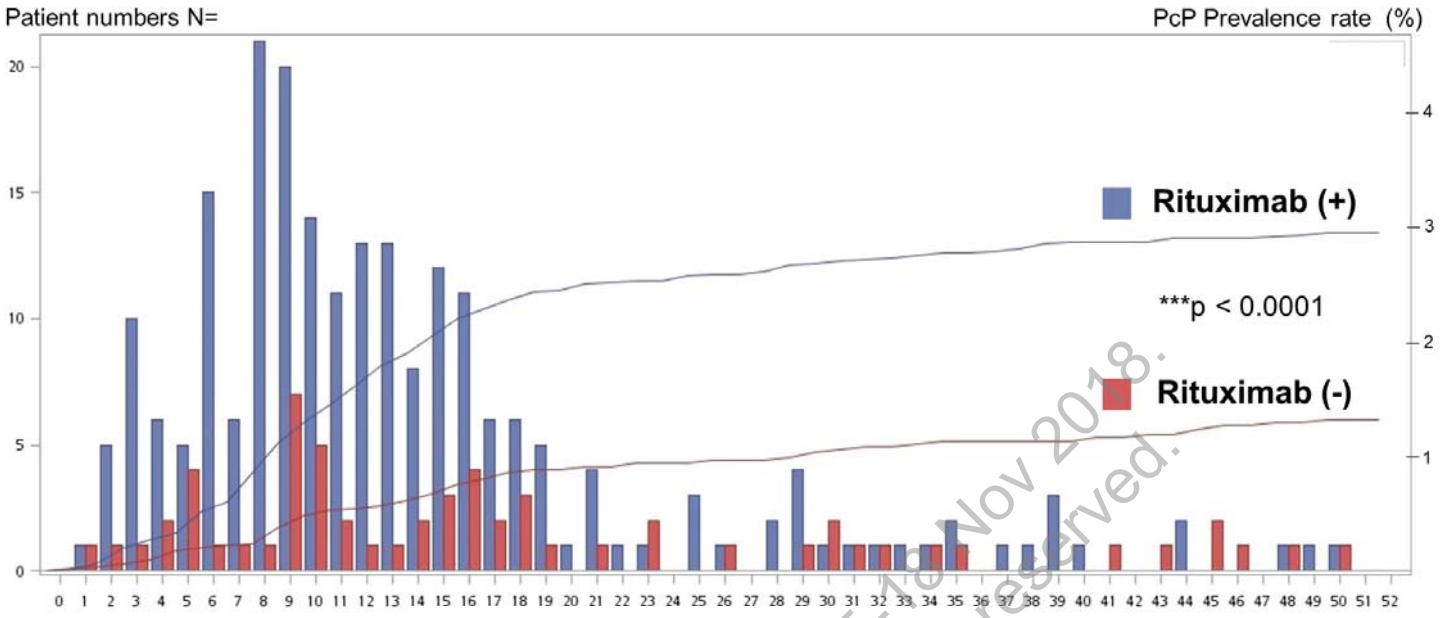
Rituximab is associated with higher PJP, not with CMV

	Rituximab (+) N=7554	Rituximab (-) N=4604	p value
P. jiroveci pneumonia (PJP)	223 (2.95%)	61 (1.32%)	<0.0001
Cytomegalovirus (CMV)	75 (0.99%)	45 (0.98%)	0.93

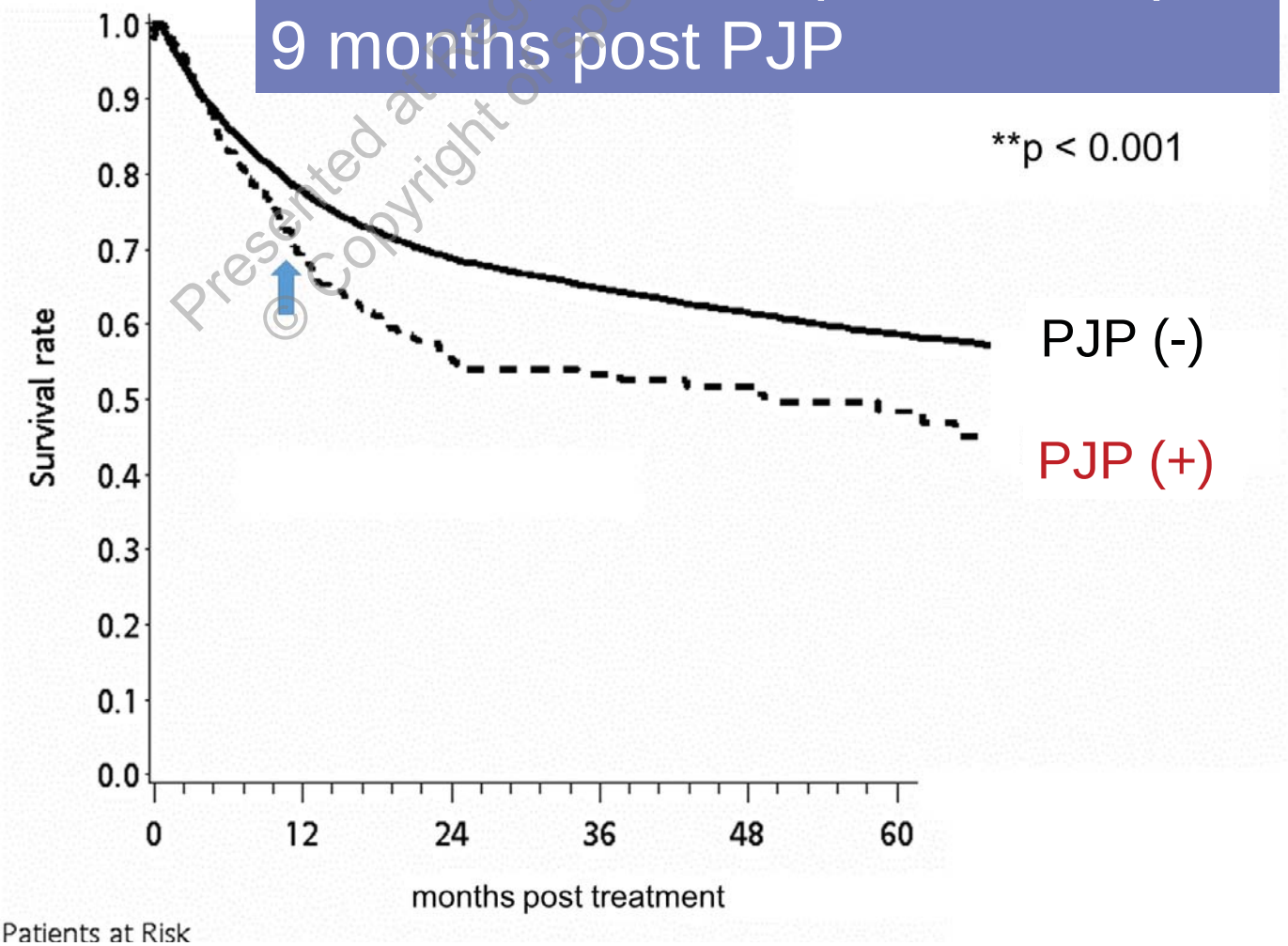
Only male gender is associated with a higher incidences of PJP

	Rituximab(+) group		
	PJP (+) N=223 (100%)	PJP (-) N=7331 (100%)	p value
Age (y)	59.4 ± 14.7	61.1 ± 16.1	0.14
Gender ratio			<0.0001
Male	150 (67.2%)	3988 (54.4%)	
Female	73 (32.7%)	3343 (45.6%)	
Chronic pulmonary disease	67 (30.0%)	2557 (34.8%)	0.13
Rheumatologic diseases	50 (22.4%)	1799 (24.5%)	0.46
Diabetes mellitus (DM)	41 (18.3%)	1653 (22.5%)	0.14
DM with chronic complications	11 (4.9%)	444 (6.0%)	0.48
Chronic kidney disease	50 (22.4%)	1799 (24.5%)	0.46

PJP mainly attack within the initial 4 months after 1st dose of rituximab



detrimental effect persisted up to 9 months post PJP



True incidence?

~ 3%

Effect of PJP?

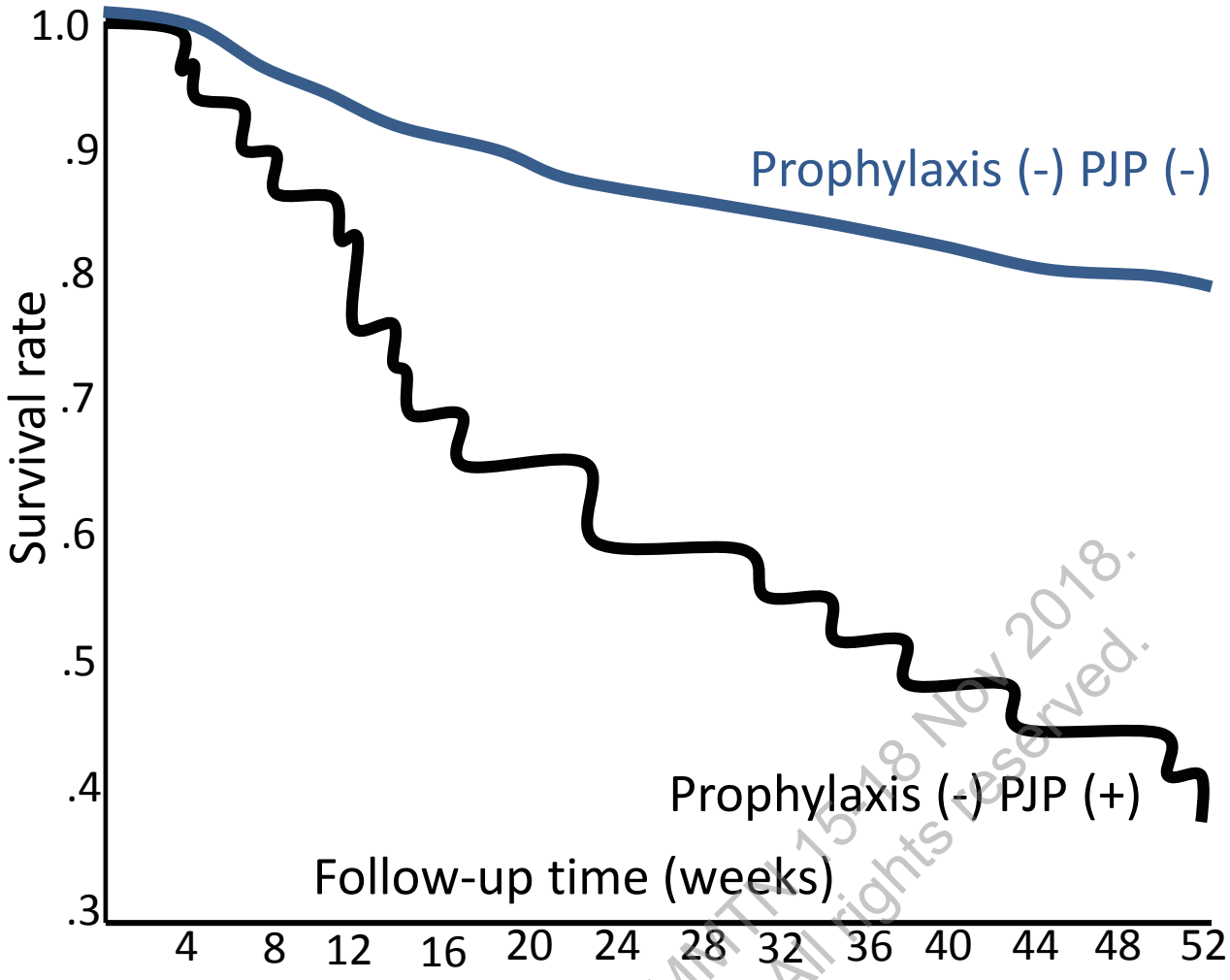
~ severe

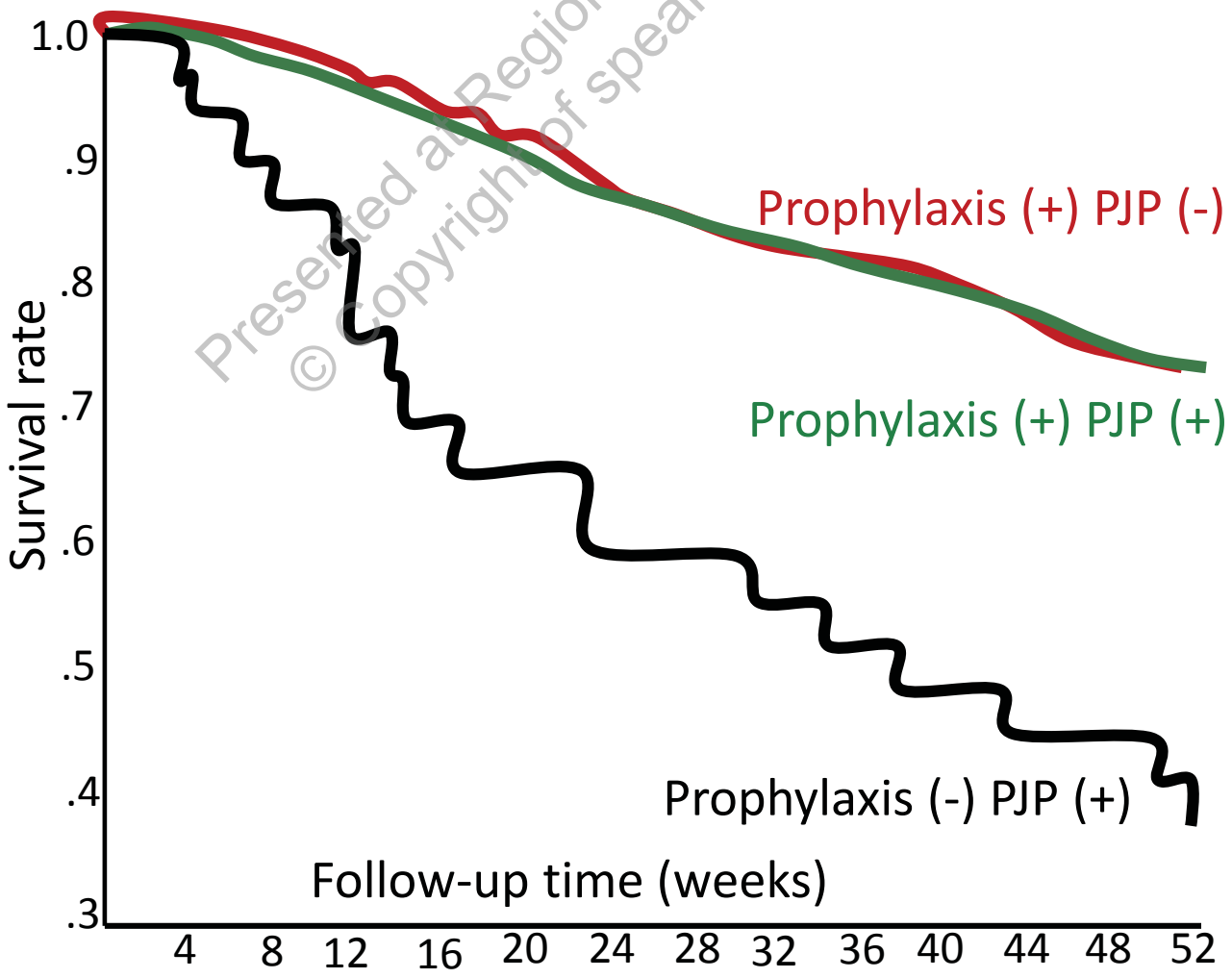
Benefits of prophylaxis outweigh adverse effect?

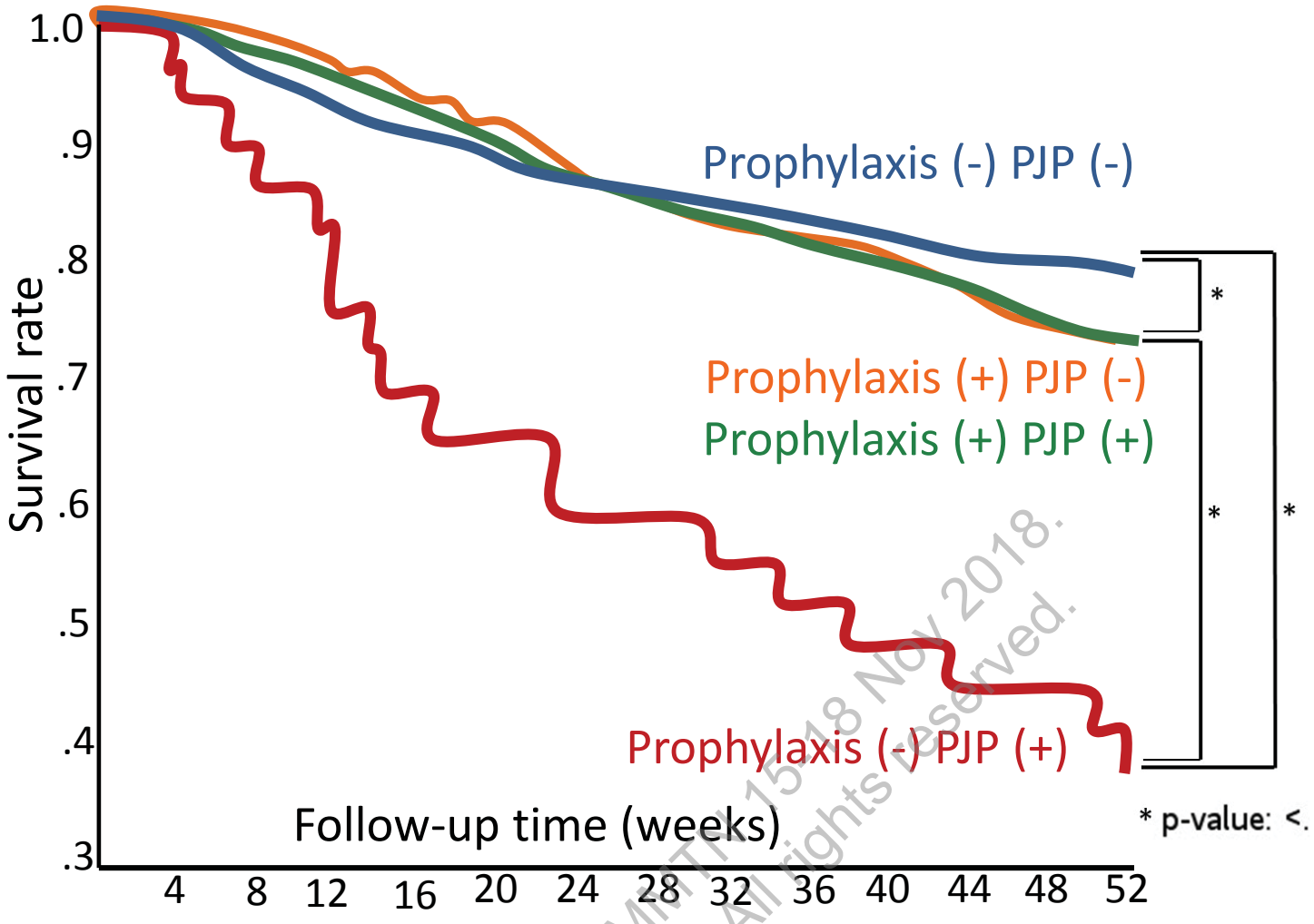
Does prophylaxis bring benefits outweighing the adverse effects?

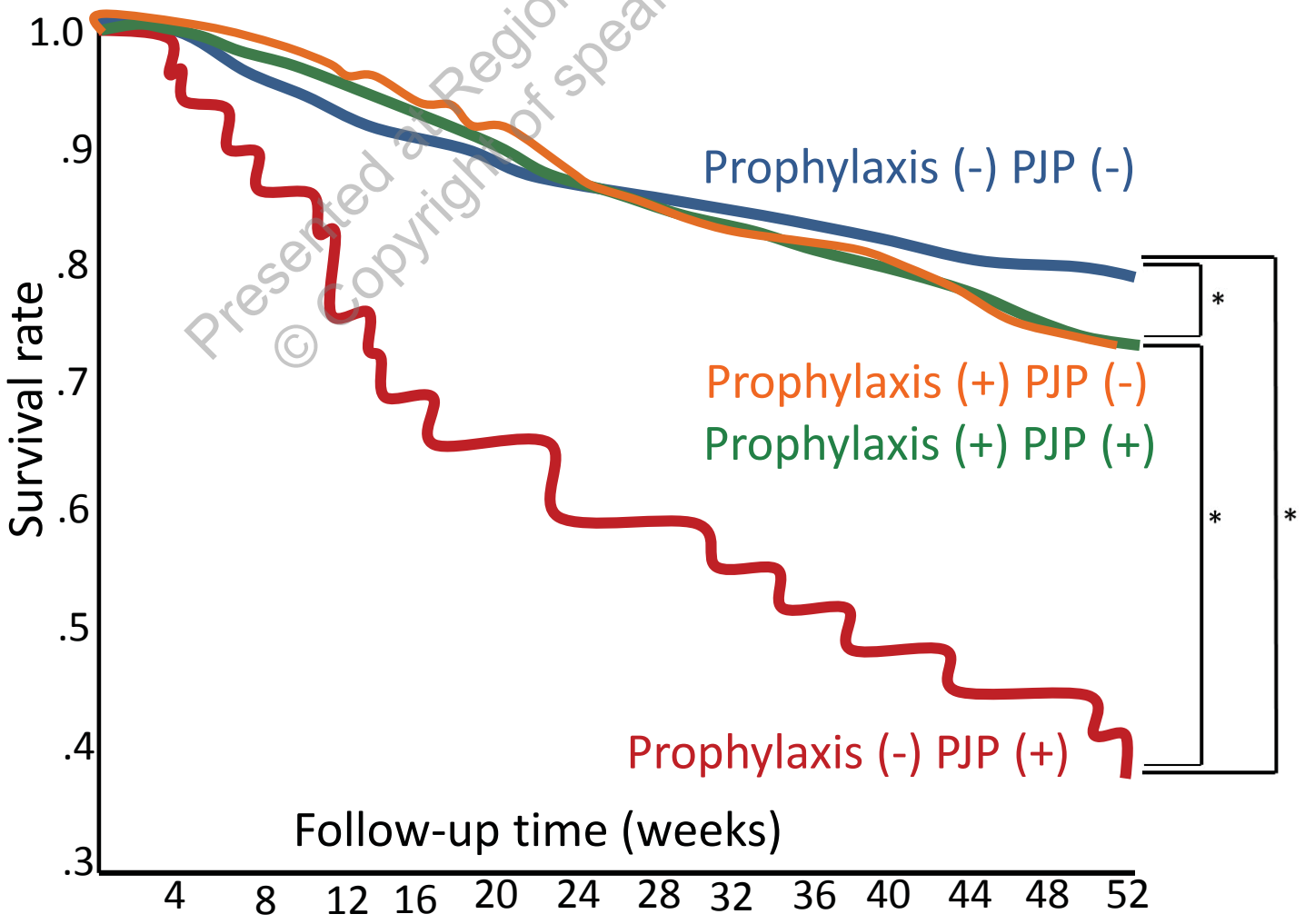
The question can be divided into several parts:

- Does PJP prophylaxis reduce PJP-related mortality?
- Does PJP prophylaxis reduce all-cause mortality?
- Is PJP prophylaxis safe and/or well-tolerated?









Does prophylaxis bring benefits outweighing the adverse effects?

The question can be divided into several parts:

- Does PJP prophylaxis reduce PJP-related mortality?
  YES
- Does PJP prophylaxis reduce all-cause mortality?
  YES
- Is PJP prophylaxis safe and/or well-tolerated?

Does prophylaxis bring benefits outweighing the adverse effects?

The question can be divided into several parts:

- Does PJP prophylaxis reduce PJP-related mortality?
  YES
- Does PJP prophylaxis reduce all-cause mortality?
  YES
- Is PJP prophylaxis safe and/or well-tolerated?

TMP-SMX prophylaxis is not safe?

- Trimethoprim-sulfamethoxazole (TMP-SMX) causes adverse drug reactions (ADRs) in 40–80% of HIV infected individuals compared to 3–5% in HIV-uninfected individuals

Cutaneous drug reactions in human immunodeficiency virus infection. *Coopman SA, Stern RS. Arch Dermatol. 1991 May; 127(5):714-7.*

Adverse effect of TMP-SMX is in dose-dependent fashion

- 21/52 (40.3%) pneumocystis pneumonia & AIDS developed an ADR.
- skin rash in 10/52 (47.6%), liver function impairment in nine (42.9%), elevated creatinine in 8 (38.1%), fever in 4 (19%), and gastrointestinal symptoms in 3 (14.3%).

- Most of the ADRs occurred within the 2 weeks of TMP/SMX therapy.
- A daily dose of TMP/SMX of ≥ 16 mg/kg (HR, 3.8; 95% confidence interval, 1.40-10.35; p = 0.009) were independently associated with

>12 tablets/day

High daily doses of trimethoprim/sulfamethoxazole are an independent risk factor for adverse reactions in patients with pneumocystis pneumonia and AIDS. ***J Chin Med Assoc.*** 2016 Jun;79(6):314-9.

Low dose of TMP-SMX is effective

First-line choice

trimethoprim/sulfamethoxazole; all other alternatives are inferior (**A-II**)

(One single-strength (80/400 mg) tablet/day or
Two tablets/day or trice a week)

Second-line choice[a]

dapsone (50 mgX2/day) (B-II)

atovaquone (1500 mg/day) (B-II)

pentamidine aerosols (300 mg once/month)

pentamidine intravenously (-)

If adverse drug reactions appear?

- Life threatening ADRs from TMP-SMX are rare.
- Adverse effects of TMP-SMX can be managed by stopping the drug.
- However, PJP is severe and can be devastating in HIV-uninfected patients.

Literature:

1. Treatment dosage (high)

2. Prolonged prophylaxis course (>2 years)

True incidence?
~ 3%
Effect of PJP?
~ severe

Benefits of prophylaxis outweigh adverse effect?
~ yes!

Last, but not the least

Adalimumab is not associated with higher risk of PJP

	Case number	
Adalimumab (anti-TNF-a)	3700	
	Case number	
PJP	3	0.08%
CMV	7	0.19%
Herpes zoster	337	9.1%
Pulmonary tuberculosis	142	3.84%
Pneumonia	617	16.68%

	Case number	
Rituximab	8191	
	Case number	
PJP	238	2.91%
CMV	106	1.29%
Herpes zoster	1133	13.83%
Pulmonary tuberculosis	230	2.81%
Pneumonia	2618	31.96%

	Case number	
Adalimumab (anti-TNF-a)	3700	
	Case number	
PJP*	3	0.08%
CMV	7	0.19%
Herpes zoster	337	9.1%
Pulmonary tuberculosis	142	3.84%
Pneumonia	617	16.68%

Conclusion

- In the era of biologic agent, PJP remains a threat for some treatments.
- PJP prophylaxis is simple and effective.
- PJP prophylaxis is needed during rituximab therapy in HIV-uninfected patients with pemphigus or non-Hodgkin lymphoma, and should last for 4~6 months

Prophylaxis of PJP outweigh the potential adverse drug effect

trimethoprim/sulfamethoxazole; all other alternatives are inferior (**A-II**)

(One single-strength (80/400 mg) tablet/day or Two tablets/day or trice a week) (B-II)

Second-line choice[a]

dapsone (50 mgX2/day) (B-II)

atovaquone (1500 mg/day) (B-II)

pentamidine aerosols (300 mg once/month)

pentamidine intravenously (-)

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Thank you for listening.

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an ISHAM working group