THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplementary appendix

1

Legend for all tables

BAL	Broncho-alveolar lavage
BMI	Body Mass Index
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
EORTC/MSG	European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group
ICU	Intensive Care Unit
IPA	Invasive pulmonary aspergillosis

Table S1: EORTC/MSG Host factors for the diagnosis of invasive pulmonary aspergillosis

EORTC-host factors for the diagnosis of invasive pulmonary aspergillosis
- Recent history of neutropenia temporally related to the onset of fungal disease (<500 neutrophils/µl for > 10 days)   - Receipt of an allogeneic stem cell transplant   - Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for > 3 weeks   - Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-alpha blockers, specific monoclonal antibodies or nucleoside analogues during the past 90 days   - Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

Table S2: Overview of included patients, number of IPA cases and diagnostic procedures performed depicted per centre

Centers	First season of inclusion	Number included	IPA case number, n (%)	BAL performed, n (%)	BAL GM performed, n (%)
1	2009	82	15 (18)	42 (51)	30 (37)
2	2009	149	39 (26)	102 (68)	43 (29)
3	2010	47	3 (6)	23 (49)	15 (32)
4	2011	52	8 (15)	21 (40)	16 (31)
5	2012	43	8 (19)	16 (37)	10 (23)
6	2012	21	4 (19)	11 (52)	9 (43)
7	2010	38	6 (16)	18 (47)	14 (37)
Total		**432**	**83 (19)**	**233 (54)**	**137 (32)**

As this was a retrospective multicentre study, the RT-PCR technique that had been in place to diagnose an influenza infection varied during the seven years of the study in each of the centres: geneXpert, FTD Respiratory pathogens but also RT-PCR test developed and validated by the local virology lab.
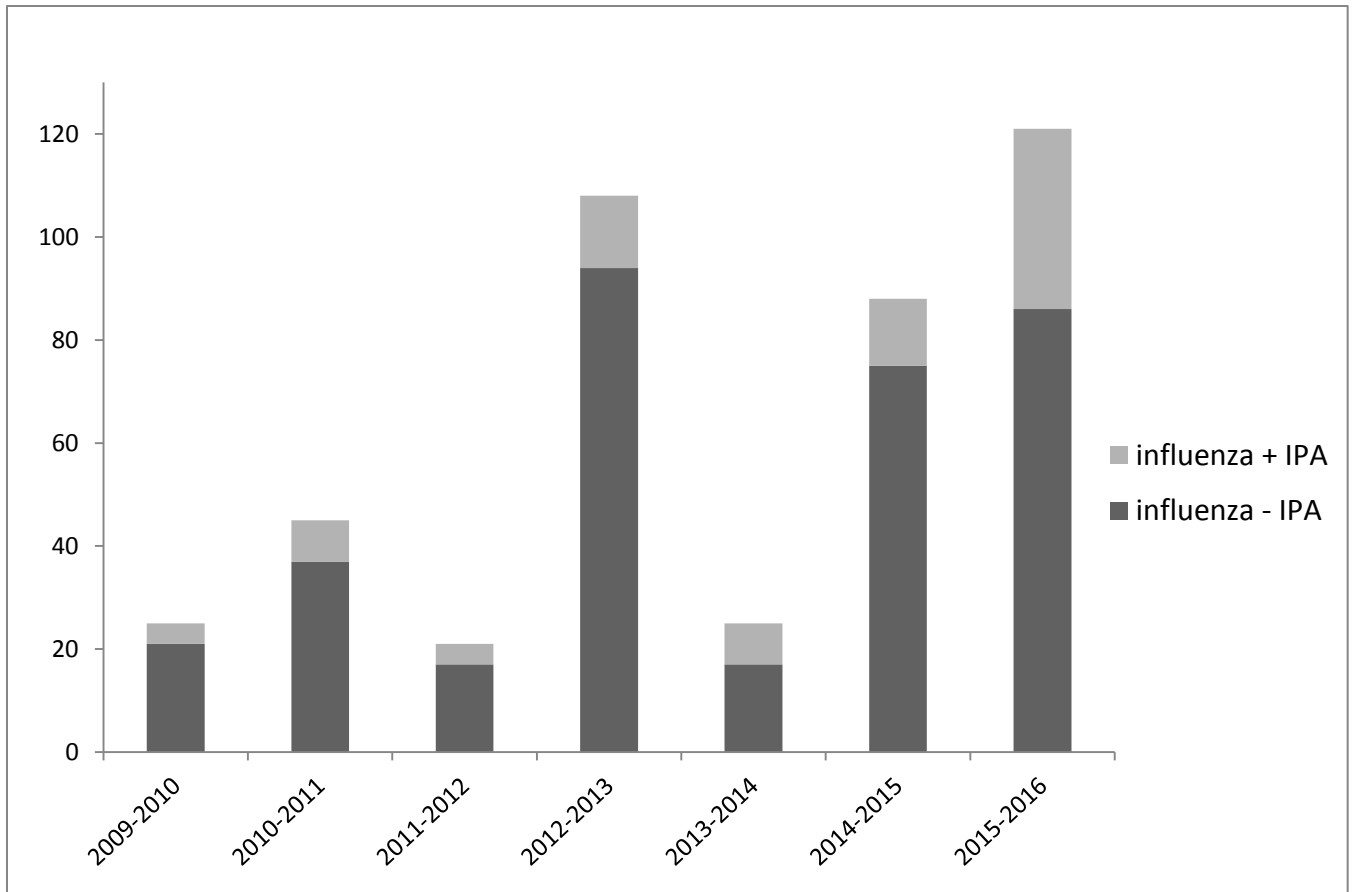
Figure S3: Overview of influenza patients admitted to ICU with and without invasive pulmonary aspergillosis (IPA) per season.

Table S4: Variables included in the multivariate analyses to determine risk factors for the development of IPA in the influenza-positive cohort with corresponding percentage of missing data

Variables in the model	Percent missing data (%)
Age	0
Center	0
Diabetes	0
Prednisone average dose mg/kg/day 28 days before ICU	5.32
APACHE II score	12.73
Sex	0
Haematological malignancy	0
Solid organ transplant	0

Table S5: Variables included in the multivariate analysis on the case-control population to determine risk factors for developing IPA with corresponding percentage of missing data.

Variables in model	Percent missing data (%)
Age	0
Influenza status	0
Center	0
Prednisone average dose mg/kg/day 28 days before ICU	5.24
Medical history of COPD	0
APACHE II score	7.78
Sex	0
BMI	3.33

Table S6: Seasonal distribution of influenza subtypes and IPA cases. Data from the annual distribution of influenza subtypes have been derived for Belgium from The Scientific Institute of Public Health (WIV-ISP) website (https://epidemio.wiv-isp.be/ID/diseases/Pages/Influenza.aspx). The data for the Netherlands have been provided by the National Influenza Centre, The Netherlands. The influenza A and B subtype distribution shown here has been calculated by excluding non-subtypable samples in the denominator.

	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016
Influenza strains Belgium							
Influenza A (%)	99	55	93	45	98	84	48
-A (H1N1) (%)	100	98	2	79	40	16	99
-A (H3N2) (%)	0	2	98	21	60	84	1
Influenza B (%)	1	45	7	55	2	16	52
-B/Yamagata(%)		7	87	96		92	3
-B/Victoria (%)		93	13	4		8	97
Influenza strains The Netherlands							
Influenza A (%)	99	65	92	73	95	84	69
-A (H1N1) (%)	100	97	1	58	41	9	98
-A (H3N2) (%)	0	3	99	42	59	91	2
Influenza B (%)	<1	35	8	27	5	16	31
-B/Yamagata (%)		5	88	94	72	99	6
-B/Victoria (%)		95	12	6	28	<1	94
Total cohort							
Influenza A (%)	92	82	81	71	100	83	86
Influenza B (%)	8	18	19	29	0	17	14
IPA (%)	4/25 (16)	8/45 (18)	4/21 (19)	13/108 (12)	8/25 (32)	12/88 (14)	34/120 (28)
- IPA influenza A	4/23 (17)	8/37 (22)	2/17 (12)	9/77 (12)	8/25 (32)	11/73 (15)	29/103 (28)
- IPA influenza B	0/2 (0)	0/8 (0)	2/4 (50)	4/31 (13)	0/0	1/15 (7)	5/17 (29)