Epidemiology of Airmen Treated with Immunosuppressive Drugs and Vaccination Concerns

Gaetan Guiu; Jonathan Monin; Anne-Pia Hamm-Hornez; Olivier Manen; Eric Perrier

BACKGROUND: Immunosuppressive treatments are increasingly prescribed in a variety of diseases. This issue concerns airmen.

METHODS: To assess the problem, we conducted an observational retrospective study in the aircrew population examined in 2014 at the Aeromedical Center of Percy Military Hospital.

RESULTS: Airmen treated with immunosuppressive drugs accounted for 0.5% of the total population ($N = 13{,}326$). Rheumatic and digestive diseases were the main etiologies, respectively 43% and 35% of cases. One-third of airmen took such medications during at least 3 yr and three-quarters of airmen were declared fit to fly, with some limitations.

DISCUSSION: Due to their working conditions, airmen are exposed to a real infectious risk, which is, however, difficult to evaluate. The risk is obviously increased by immunosuppressive drugs and may affect flight safety. Aeromedical evaluation should consider this problem. Vaccination plays a central role in the prevention of infectious risk. Based on French recommendations, we propose a vaccination schedule for these particular patients.

KEYWORDS: flight safety, infectious risk, immunization schedule.

Guiu G, Monin J, Hamm-Hornez A-P, Manen O, Perrier E. *Epidemiology of airmen treated with immunosuppressive drugs and vaccination concerns*. Aerosp Med Hum Perform. 2018; 89(4):377–382.

Immunosuppressive drugs seem to be prescribed more and more for several diseases; moreover, new drugs appear regularly and are used earlier in the therapeutic strategy. Three classes of immunosuppressive drugs are classically distinguished: glucocorticoids, and chemical and biological immunosuppressants.[5] For glucocorticoids, immunosuppression appears for a treatment of more than 2 wk at greater than or equal to 10 mg of prednisone equivalent per day in adults[8,15] and during 3 mo after a bolus of high dose.[8,1,13] Chemical immunosuppressants act on cellular immunity and on humoral immune response.[2] Biological immunosuppressants are also called biotherapies or targeted therapies because they are specific to an antigen and have a selective action on it. The most commonly used are those that target TNF-alpha, which plays an important role in anti-infectious defense. Immunosuppressive therapies can lead to different side effects which vary from one drug to another; nevertheless, infectious risk is common[4,7,17] and cannot be neglected.[22,26,28] It is all the more important that the treatment combines several immunosuppressive drugs, acting at different steps of the immune response.[27] Immune deficiency is usually difficult to quantify and may concern humoral and/or cellular immune response.[15] With glucocorticoids, the relative infectious risk can be doubled compared to the general population.[9] They are mainly banal bacterial infections, but also intracellular infections, viral infections, tuberculosis reactivation, etc.[12] The infectious risk due to chemical immunosuppressants varies depending on the drug. For example, methotrexate increases the risk of bacterial infections mainly in the upper airways and skin.[28] In the case of anti-TNF-alpha therapy, the risk of infection is doubled,[7,22] with mainly respiratory pyogenic germs, cutaneous infections, and urinary infections.

This issue concerns aircrew members, many of whom are exposed to an additional infectious risk because of their working conditions. Their health is at stake, but also their operational capacities and flight safety. In order to appreciate the situation,

From the Aeromedical Center of Percy Military Hospital, Clamart, France, and the French Military Health Service Academy—Ecole du Val de Grace, Paris, France.

This manuscript was received for review in January 2017. It was accepted for publication in December 2017.

Address correspondence to: Dr. Gaetan Guiu, Aeromedical Center of Percy Military Hospital, 101 avenue Henri Barbusse, Clamart, Hauts de Seine 92141, France; gaetanguiu@hotmail.com.

DOI: https://doi.org/10.3357/AMHP.4820.2018

we were interested in aircrew members treated with immunosuppressive drugs followed up at the aeromedical center of Percy Military Hospital (AeMC Percy).[21]

METHODS

We carried out a retrospective observational study on aircrew members' medical files examined at AeMC Percy in 2014. The objectives were to collect the demographic characteristics of the population treated with immunosuppressive drugs, the pathologies, the treatments, their duration and possible side effects, particularly infectious diseases, and the aeromedical fitness decision, and to calculate their percentages. We excluded airmen treated for cancer and those with a very short-term treatment.

RESULTS

There were 13,326 aircrew members who presented for an aeromedical evaluation in 2014 at AeMC Percy. Of 112 airmen treated with immunosuppressive drugs, 44 were excluded from our data collection because they were treated for cancer or very short-term treatment. The characteristics of the 68 airmen treated with immunosuppressive treatment included in our study are shown in **Table I**.

Professional pilots account for 25% of the cases, military pilots 16%, commercial aircrews 21%. Military air controllers and private pilots represent, respectively, 23% and 12%. The diseases justifying the introduction of an immunosuppressive therapy are mainly rheumatic and digestive. Rheumatic diseases account for 43% of the causes of treatment by immunosuppressant, with a majority of ankylosing spondylitis, cases of rheumatoid arthritis, and psoriatic arthritis. Digestive pathologies account for 35% of cases: mainly intestinal chronic inflammatory diseases (Crohn's disease and ulcerative colitis), but also liver transplantations. The other causes are uro-nephrology with nephropathies and renal transplantations, neurological with four cases of multiple sclerosis, pneumological with sarcoidosis, and systemic with, for example, two cases of systemic lupus erythematosus.

Immunosuppressive drugs used were mainly glucocorticoids (67%), followed by methotrexate (27%), anti-TNF alpha (23%), cyclosporine and its relatives (18%), and azathioprine (15%) (**Fig. 1**). In 47% of cases, treatment involves or has involved the use of at least two immunosuppressive drugs, in association or in replacement (in the case of failure or intolerance of a drug). Concerning the duration of treatment, in 25% of cases, it was less than 6 mo, in almost 44% it was more than 2 yr, and in 20% of cases, it exceeded 5 yr (**Fig. 2**).

Table I. Demographic Characteristics of the 68 Airmen Treated with Immunosuppressive Drugs Seen at AeMC Percy in 2014 ($N = 68$).

DEMOGRAPHIC	NUMBER (%)
Average age	41.5 yr
Gender ratio (M/W)	2.7
Number of civilians (%)	43 (63)
Number of professional pilots (%)	17 (25)
Number of private pilots (%)	8 (11.7)
Number of military pilots (%)	11 (16.2)
Number of air traffic controllers (%)	16 (23.5)
Number of flight engineers (%)	2 (3)
Number of commercial aircrew (%)	14 (20.6)

This has an impact on the occurrence of side effects. Such effects were reported by 16 airmen (23%), but no infection was reported (**Table II**). Regarding aeromedical fitness decisions, in most cases (75%) a certificate was issued by the licensing authority with limitations: essentially a time limitation (82%), the presence on board of a security pilot (50% of pilots), and an overseas unfitness (22%). The geographical limitation concerned all military airmen for whom overseas missions were considered too risky. There was no geographical limitation for civilians, especially commercial aircrew and professional pilots. In 25% of cases, airmen were declared unfit because of the disease's severity, which was incompatible with their aeronautical function (71%), because of the treatment (18%), and because of a depressive state.

DISCUSSION

In our study, airmen treated with immunosuppressive drugs represent a small proportion (0.5%) of the population. Nevertheless, it is not an exceptional situation. If no additional infectious risk was found in our study, our collection probably suffers from an under-reporting bias due to the context of aeromedical fitness assessment.

Aircrew members are exposed to an infectious risk because of their working conditions. Civilian airmen, particularly commercial aircrew, are in more or less prolonged contact with passengers depending on the duration of the flight and are exposed to airborne diseases, for example. In addition, airmen working on medium and long-haul flights or those expatriated may be exposed to tropical diseases; this is also true for military airmen deployed to tropical countries, particularly in Africa. The infectious risk is variable and difficult to estimate, but it depends on the length of stay or stopover, on-site activities (travel in the field, stay at the hotel, etc.), and conditions of life. Air traffic controllers are not exposed to the same infectious risk as aircrew members, unless they are sent to a tropical country. Nevertheless, their infectious risk is statistically greater than the general population, in particular concerning airborne infections.[12,26,28]

The infectious risk for the airmen treated with immunosuppressive drugs and its potential impact on operational abilities should be considered during an aeromedical evaluation. These patients are immune-compromised and the prevention of infections is essential in order to reduce morbidity. This prevention combines several aspects: patient education and awareness, screening and patient follow-up, sometimes preventive anti-infectious treatment, and vaccine prophylaxis. It is necessary on the one hand to take into account the recommendations for

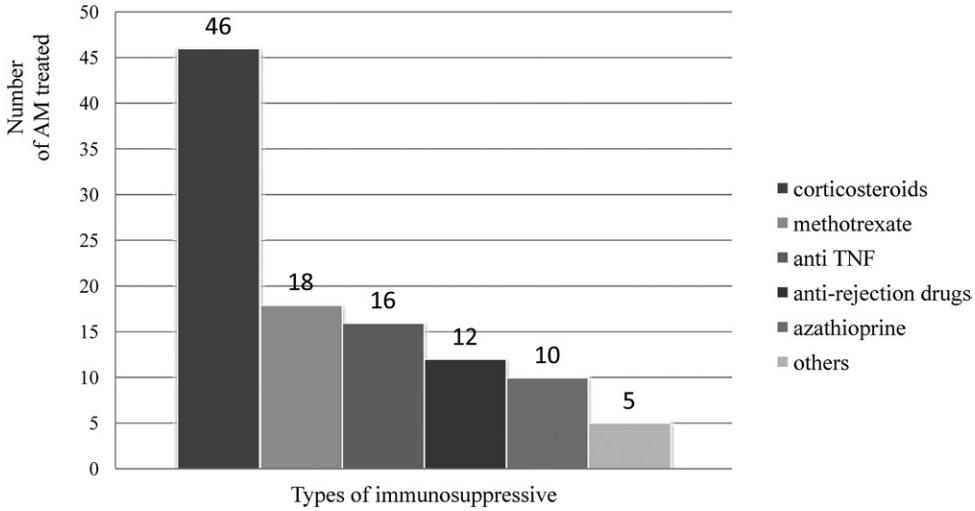

Fig. 1. Immunosuppressive drugs used.

patients treated with immunosuppressive drugs[15] and on the other hand those for travelers.[14] As such, airmen may be referred to a travel medicine consultation, which may lead to the prescription of a vaccination prophylaxis, a possible malaria chemo-prophylaxis, as well as adapted advice.

Vaccination is one of the pillars of disease prevention, even more so in case of an immunosuppression. This vaccine prevention must be carried out before the beginning and also under treatment and, therefore, sometimes for life (e.g., a graft). At this time, there is no mention of vaccination in the European Regulations.[25] Civilian airmen must, however, comply with international health regulations,[29] particularly with regard to vaccination against yellow fever. The recommendations of the French High Council for Public Health concerning travel medicine do not specifically target aircrews except for the influenza vaccination, which is recommended to them.[13] For military airmen, the infectious risk is taken into account in the same way as for other military personnel. In the French Armies, vaccinations are statutory and mandatory according to a sufficiently complete vaccination schedule, updated annually on the basis of the civil calendar and taking into account the particularities of the military (ministerial circular n°510,114/DEF/DCSSA/PC/ERS/EPID of 23 may 2016). The aim is to minimize the health risks associated with seasonal infections, community life, and deployments in foreign countries under sometimes rough conditions in order to maintain operational capacities.

Fig. 3 summarizes the immunization schedule used in the French armed forces[6] in 2016. Taking into account the recommendations, the infectious risk associated with an immunosuppressive treatment, and constraints related to the airmen's functions, it is possible to propose a vaccination schedule, as summarized in **Table III**. Inactivated vaccines can be administered even under immunosuppressive therapy,[2,3] although there is a risk of their immunogenicity decreasing.[15] It is recommended to avoid vaccination within 6 mo after organ transplantation, so it is important to update the vaccinations beforhand.[13] Recalls for vaccination against diphtheria-tetanus-poliomyelitis must be decennial[15] and, in the case of a stay in the circulation zone of the wild polio virus (Afghanistan, Pakistan, Nigeria),[7] it is recommended to recall for poliomyelitis if the last vaccination is more than 1 yr old.[13,14,30] Vaccination against hepatitis B is recommended, especially when traveling in areas of high or medium endemicity[13] (Africa, Asia, South America, Central Europe, Russia, Mediterranean region) and in case of treatment by anti-TNF-alpha, if prevaccine serology is negative.[15,22] Vaccination against pneumococcus is recommended before starting immunosuppressive therapy,[23] according to the prime-boost regime, which consists in one injection with 13-valences conjugated vaccine followed 2 mo later by one injection with 23-valences unconjugated vaccine.[15] Then a booster injection with the unconjugated vaccine every 5 yr is recommended for prolonged treatment.[15,22] Annul vaccination against seasonal influenza is strongly recommended[15,18,24] (inactivated vaccine only).

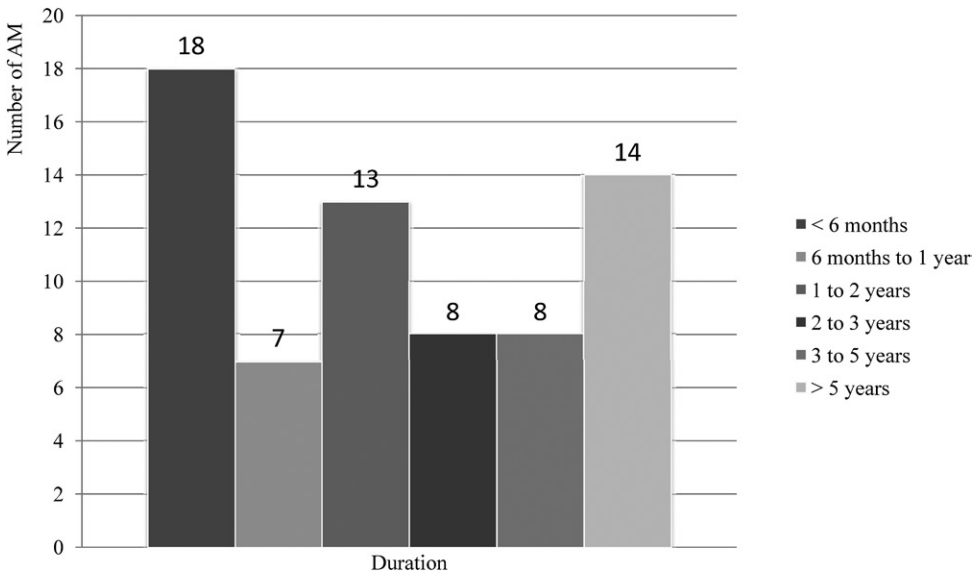

Fig. 2. Duration of immunosuppressive therapy.

Table II. Side Effects Reported by Aircrew Treated with Immunosuppressive Drugs ($N = 16$).

GLUCOCORTICOIDS ($N = 6$)	METHOTREXATE ($N = 4$)	AZATHIOPRINE ($N = 3$)	ANTI-TNF-ALPHA ($N = 3$)
Sleep disorders, cognitive impairment (3)	Hepatic toxicity (2)	Leucopenia (2)	Multiple sclerosis (1)
Cushing's syndrome (1)	Digestive disorders (1)	Digestive disorders (1)	Uveitis (1)
Secondary diabetes (1)	Toxidermia (1)		Migraine (1)

Vaccination against hepatitis A is advised for airmen who are exposed to countries with lower levels of hygiene.[1,11] Vaccination against invasive meningococcal infections with ACYW tetravalent vaccine is recommended in the case of a stay in an at-risk or epidemic zone, particularly in sub-Saharan Africa from Senegal to Ethiopia from December to June.[13] Despite limited effectiveness, we strongly recommend vaccination against typhoid fever in case of repeated stopovers or stays in the Indian subcontinent and in Africa. Vaccinations against Japanese encephalitis, tick-born encephalitis, leptospirosis, rabies, and cholera are not recommended specifically for airmen treated with immunosuppressive drugs, but only in the case of an at-risk stay, in accordance with the recommendations for travelers.

Live-attenuated vaccines, when administered to an immunecompromised patient, are at risk of causing the disease against which they are supposed to protect. That is why vaccination should be completed at least 4 wk before immunosuppression.[12] Except after solid organ transplantation, administration of such vaccines may be possible during treatment, but this requires a therapeutic window of several months.[10] In the case of hematopoietic stem cell transplantation, it is necessary to wait at least 2 yr after the end of the immunosuppressive therapy.[15] BCG vaccine is formally contraindicated in these patients[15] because of the risk of loco-regional and generalized infection. Updating of the measles-mumps-rubella (MMR) vaccination is strongly recommended according to the general population vaccination schedule.[10,16] It includes two doses of MMR vaccine, 1 mo apart, for people born after 1980. Vaccination against yellow fever is recommended in the absence of prior vaccination before starting immunosuppressive therapy.[15] Indeed, airmen are potentially likely to fly to areas at risk. Nonvaccination against yellow fever will impose geographical limitations. Subsequently, only one booster dose will be recommended 10 yr after primary vaccination in the absence of immunosuppressive therapy.[12] Varicella vaccination is also recommended before immunosuppressive therapy in the absence of a notified history of varicella or, if so, in the case of negative serology.

Finally, the traceability of vaccinations is essential for such patients. It may be worthwhile to establish and update an electronic vaccination record that can be accessed via internet on a computer, but also on a smartphone thanks to a dedicated application. The advantages of such an "e-vaccination-record" are its permanent availability, making it possible to overcome the forgetfulness or the loss of the paper booklet, with the existence of automatic reminders of the next deadline allowing a better application of the vaccination recommendations and the sharing of information between the various medical actors in respect of medical secrecy. [19,20]

In conclusion, an immunosuppressive treatment increases the risk of infection depending on the drugs and the duration of the treatment. The proportion of aircrew members treated with immunosuppressive drugs is small but not negligible; treatment is often prolonged and can associate or comprise several successive drugs. It is essential to take into account the infectious risk associated with the conditions of employment such as a flight of several hours in an aircraft cabin with many passengers or stops and more or less prolonged stays in tropical countries. Vaccine prophylaxis is primary in the prevention of disease and should be carried out as much as possible before starting treatment and should be regularly updated. Aeromedical examiners have a role to play in monitoring vaccination status during revision visits. This monitoring will be facilitated with the assistance of an electronic vaccination record that should be developed, especially for these patients.

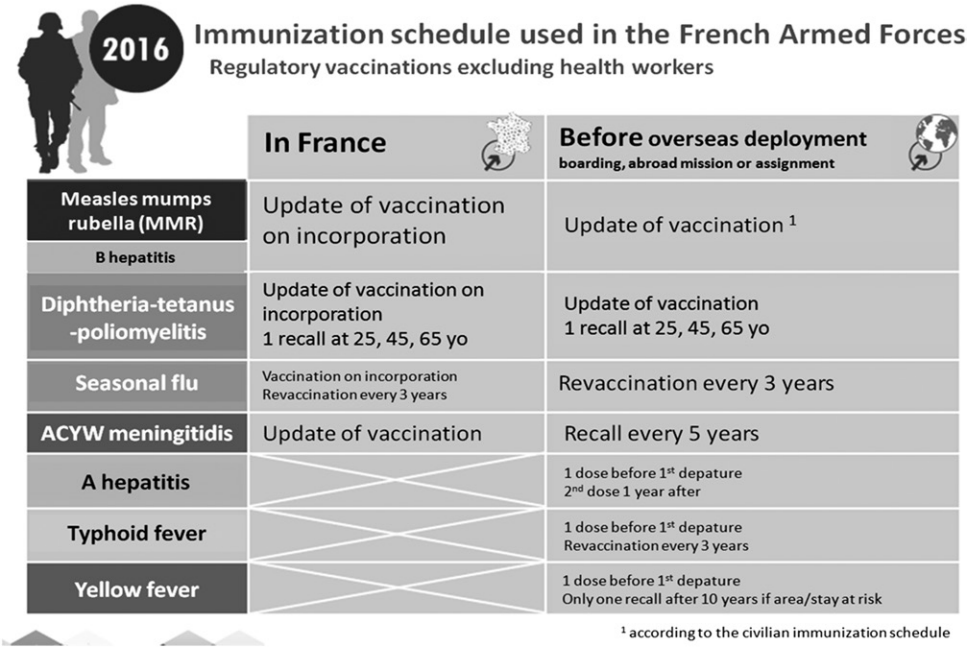

Fig. 3. Synoptic presentation of the 2016 immunization schedule used in the French armed forces.[6]

Table III. Immunization Schedule for Aircrew Treated with Immunosuppressive Drugs.*

	VACCINE:	VACCINAL SCHEME AND OBSERVATIONS
Inactivated vaccines	Diphtheria-tetanus - poliomyelitis	1 dose every 10 yr. Recall for poliomyelitis if the last vaccination is more than 1 yr old and travel in country where wild virus is circulating (Afghanistan, Pakistan, Nigeria…) (dTP vaccine or monovalent poliomyelitis vaccine).
	Pertussis	1 dose in adulthood.
	Hepatitis B	Three-dose scheme (20 μg): initially, 1 mo later, and 6th month.
	Hepatitis A	Two doses spaced six months apart.
	Pneumococcus	Initial scheme: 1 dose of 13 valences conjugated vaccine and then, 2 mo after, 1,dose of 23 valences nonconjugated vaccine. Recall every 5 yr with the 23-valent nonconjugated vaccine.
	Seasonal flu	One dose every year (only inactivated vaccine).
	Invasive meningococcal infections	One dose of ACYW tetravalent vaccine. Recall every 5 yr. In the absence of ACYW vaccination, monovalent C vaccine is recommended up to 24 yr of age.
	Typhoid fever	One dose. Recall every 3 yr if necessary.
Live attenuated vaccines	Measles-mumps-rubella (MMR)**	Two doses spaced 1 mo apart for persons born after 1980; for those born before 1980, a single dose of MMR may be sufficient.
	Yellow fever**	A recall 10 yr after primary vaccination is recommended.
	Varicella**	Two doses spaced one month apart.
	Vaccines against tuberculosis and rotavirus are contraindicated	

* Including immunosuppressive-dose glucocorticoids: more than 10 mg · d^{-1} prednisone-equivalent (PE) in adults and 3 mo after a bolus of more than 0.5 g PE.
** Vaccination can be done, but before starting the immunosuppressive treatment or after a therapeutic window of several months.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Nicolas Huiban, Dr. Vincent Beylot, Dr. Jean-François Oliviez, Dr. Dominique Dubourdieu, and Dr. Jacques Deroche.
The authors have declared no conflicts of interest.

Authors and affiliation: Gaetan Guiu, Dr. med., Jonathan Monin, Dr. med., Anne-Pia Hamm-Hornez, Dr. med., Olivier Manen, Pr. med., and Eric Perrier, Pr. med., Aeromedical Center of Percy Military Hospital, Clamart, France.

REFERENCES

1. Askling HH, Rombo L, van Vollenhoven R, Hallén I, Thörner A, et al. Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study. Travel Med Infect Dis. 2014; 12(2):134–142.
2. Bingham 3rd CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum. 2010; 62(1):64–74.
3. Bingham 3rd CO, Rizzo W, Kivitz A, Hassanali A, Upmanyu R, Klearman M. Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: results of a randomised controlled trial (VISARA). Ann Rheum Dis. 2015; 74(5):818–822.
4. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006; 295(19):2275–2285.
5. Brousse C, Somogyi A, Bletry O. Les immunosuppresseurs [Immunosuppressive therapies]. Concours med. 2001; 123-07:451–454.
6. Calendrier vaccinal dans les armees, 2016 [Vaccination schedule for the French armed forces, 2016]. [Accessed 30/11/2016.] Available from http://www.defense.gouv.fr/content/download/464757/7396176/file/cartevaccins6.pdf [in French].
7. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007; 56(4):1125–1133.
8. Danziger-Isakov L. Kumar D and the AST infectious diseases community of practice. Vaccination in solid organ transplantation. Am J Transplant. 2013; 13(s4):311–317.
9. Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. Ann Rheum Dis. 2007; 66(3):308–312.
10. Frazier-Mironer A. Vacciner les patients sous immunosuppresseurs ou biothérapies? [Should patients receiving immunosuppresive drugs or biotherapies be vaccinated?] Rev Prat. 2015; 65(2):156–158.
11. Haut Conseil de la Santé Publique. Avis relatif aux recommandations de vaccination préventive ciblée contre l'hépatite A [High Council for Public Health. Statement about recommendations for anti-hepatitis A vaccination]. February 2009. [Accessed 30/11/2016.] Available from http://www.hcsp.fr/docspdf/avisrapports/hcspa20090213_HepARecomm.pdf.
12. Haut Conseil de la Santé Publique. Calendrier des vaccinations etrecommandationsvaccinales 2017 (High Council for Public Health. Vaccination schedule and recommendations 2017). [Accessed 6/10/2017.] Available from http://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinations_2018.pdf.
13. Haut Conseil de la Santé Publique. Recommandations sanitaires pour les voyageurs, 2017. Bulletin épidémiologiquehebdomadaire [High Council for Public Health.Health recommendations for travelers, 2017]. [Accessed 6/10/2017.] Available from http://invs.santepubliquefrance.fr/Publications-et-outils/BEH-Bulletin-epidemiologique-hebdomadaire/Archives/2017/BEH-hors-serie-Recommandations-sanitaires-pour-les-voyageurs-2017.
14. Haut Conseil de la Sante Publique. Vaccination de rappel contre la poliomyélite. Recommandations pour les voyageurs [High Council for Public Health. Vaccination recall against poliomyelitis, recommendations for travelers]. July 2014. [Accessed 30/11/2016.] Available from http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=446.
15. Haut Conseil de la Santé Publique. Vaccination des personnes immunodéprimées ou asplèniques. Recommandations, 2nd edition [High Council for Public Health. Vaccination recommendations for immunocompromised patients]. December 2014. [Accessed 30/11/2016.] Available from http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=504.
16. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. JAMA. 1992; 267(9):1237–1241.

17. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α–neutralizing agent. N Engl J Med. 2001; 345(15):1098–1104.
18. Kobashigawa T, Nakajima A, Taniguchi A, Inoue E, Tanaka E, et al. Vaccination against seasonal influenza is effective in Japanese patients with rheumatoid arthritis enrolled in a large observational cohort. Scand J Rheumatol. 2013; 42(6):445–450.
19. Koeck JL, Baratchart BA, Beguerie P, Brunetaud J, Koeck JD, et al. Le carnet de vaccination électronique intelligent et partagé de Mesvaccins.net [Mesvaccins.net electronic vaccination record]. [Accessed 30/11/2016.] Available from http://inpes.santepubliquefrance.fr/jp/cr/pdf/2011/session6/Poster-Koeck.pdf.
20. Mon carnet de vaccination electronique [My vaccination record]. [Accessed 30/11/2016.] Available from http://www.mesvaccins.net [in French].
21. Monin J, Aletti M, Hornez A-P, Guiu G, Huiban N, et al. Immune modulating drugs and aeromedical fitness. 87th ASMA Annual Scientific Meeting, Atlantic City, April 24–28 2016. Alexandria (VA): Aerospace Medical Association; 2016.
22. Morelon E, Touraine JL. Complications infectieuses liées à l'immunosuppression dans la transplantation d'organe [Infectious complications due to immunosuppression in organ transplantation]. Rev Prat. 2007; 57:1677–1686.
23. Mori S, Ueki Y, Akeda Y, Hirakata N, Oribe M, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. Ann Rheum Dis. 2013; 72(8):1362–1366.
24. Mutsch M, Tavernini M, Marx A, Gregory V, Lin YP, et al. Influenza virus infection in travelers to tropical and subtropical countries. Clin Infect Dis. 2005; 40(9):1282–1287.
25. Regulation no. 1178/2011 of 3 November 2011. Laying down technical requirements and administrative procedures related to civil aviation aircrew pursuant to Regulation (EC) No. 216/2008 of the European Parliament and of the Council. [Accessed 30/11/2016.] Available from http://easa.europa.eu/document-library/regulations/commission-regulation-eu-no-11782011.
26. Segal BH, Sneller MC. Infectious complications of immunosuppressive therapy in patients with rheumatic diseases. Rheum Dis Clin North Am. 1997; 23(2):219–237.
27. Toruner M, Loftus EV, Harmsen WS, Zinsmeister AR, Orenstein R, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology. 2008; 134(4):929–936.
28. van der Veen MJ, van der Heide A, Kruize AA, Bijlsma JW. Infection rate and use of antibiotics in patients with rheumatoid arthritis treated with methotrexate. Ann Rheum Dis. 1994; 53(4):224–228.
29. WHO. International travel and health, 2012. 2014 partial update. [Accessed 30/11/2016.] Available from http://www.who.int/ith/en/.
30. WHO. Statement on the Seventh IHR Emergency Committee meeting regarding the international spread of poliovirus, nov 2015. [Accessed 30/11/2016.] Available from http://www.who.int/mediacentre/news/statements/2015/ihr-ec-poliovirus/fr/.