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# Ability of physicians to diagnose influenza and usefulness of a rapid influenza antigen test in febrile returning travelers: A randomized controlled trial

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Febrile returning travelers;
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**Summary** *Background:* Fever is a frequent cause of medical consultation among returning travelers. The objectives of this study were to assess whether physicians were able to identify patients with influenza and whether the use of an influenza rapid diagnostic test (iRDT) modified the clinical management of such patients.
*Methods:* Randomized controlled trial conducted at 2 different Swiss hospitals between December 2008 and November 2012. Inclusion criteria were 1) age ≥18 years, 2) **documented fever of ≥38 °C or anamnestic fever + cough or sore throat** within the last 4 days, 3) illness occurring within 14 days after returning from a trip abroad, 4) no definitive alternative diagnosis. Physicians were asked to estimate the likelihood of influenza on clinical grounds, and a single nasopharyngeal swab was taken. Thereafter patients were randomized into 2 groups: i) patients with iRDT (BD Directigen A + B) performed on the nasopharyngeal swab, ii) patients receiving usual care. A quantitative PCR to detect influenza was done on all nasopharyngeal

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swabs after the recruitment period. Clinical management was evaluated on the basis of cost of medical care, number of X-rays requested and prescription of anti-infective drugs.
*Results:* 100 eligible patients were referred to the investigators. 93 patients had a naso-pharyngeal swab for a PCR and 28 (30%) swabs were positive for influenza. The median probability of influenza estimated by the physician was 70% for the PCR positive cases and 30% for the PCR negative cases ($p < 0.001$). The sensitivity of the iRDT was only 20%, and specificity 100%. Mean medical cost for the patients managed with iRDT and without iRDT were USD 581 (95%CI 454—707) and USD 661 (95%CI 522—800) respectively. 14/60 (23%) of the patients managed with iRDT were prescribed antibiotics versus 13/33 (39%) in the control group ($p = 0.15$). No patient received antiviral treatment.
*Conclusion:* Influenza was a frequent cause of fever among these febrile returning travelers. Based on their clinical assessment, physicians had a higher level of suspicion for influenza in PCR positive cases. The iRDT used in this study showed a disappointingly low sensitivity and can therefore not be recommended for the management of these patients.
**Trial registration**: ClinicalTrials.gov NCT00821626.


## 1. Introduction

Fever is a frequent cause of medical consultations among returning travelers. Among 24,920 travelers consulting a GeoSentinel clinic, 28% indicated fever as the main reason for seeking medical care [1]. The differential diagnosis of such febrile illnesses is particularly wide, as it includes imported and locally acquired infectious diseases. Previous studies have shown that influenza is a frequent cause of fever in travelers. A sero-epidemiological study showed that 27 of 211 patients (12.8%) with fever during or shortly after travel developed antibodies against influenza [2]. 6.2% of the 211 patients had a ≥4-fold increase of antibody titers against influenza. Another study showed that 13% of travelers with influenza-like symptoms had a positive test for influenza either by culture or by PCR [3].

To our knowledge most medical centers in Switzerland do not test febrile returning travelers for influenza. This is contrary to some clinical practice guidelines about influenza diagnosis. For example the guidelines of the Infectious Diseases Society of America recommend testing febrile patients who return from countries where the influenza virus may be circulating [4].

Viral culture has long been the gold standard to detect influenza virus, but its long turn-around time (≥3 days) reduces its usefulness in daily practice. PCR is a technology which has an even higher sensitivity than viral culture to detect influenza virus. Its availability is however often limited to larger laboratories and cost is relatively high. Rapid diagnostic tests for influenza are lateral flow immunochromatographic assays, and they overcome some of above-mentioned problems. They are easy to perform, give an answer within 30 min and they are relatively cheap. They can be performed on a variety of specimens, such as nasopharyngeal swabs or aspirates, pharyngeal swabs and sputa. They should ideally be performed within the first 4 days of symptom onset, as afterwards the viral shedding decreases. There are at least 20 different influenza rapid tests, which are commercialized, but their use has been controversial because of limited sensitivity.

The aims of this study were 1) to investigate whether physicians are able to identify febrile travelers with influenza on the basis of their clinical assessment; 2) to evaluate the usefulness of an influenza rapid antigen test (iRDT) for the management of such cases.

## 2. Methods

Patients aged ≥18 years were recruited from the outpatient clinic of the University Hospital of Lausanne and the outpatient clinic of the Swiss Tropical and Public Health Institute in Basel between December 2008 and November 2012. If the patients reported returning from an international trip within the last 14 days, had an influenza-like illness for not more than 4 days, and no other obvious diagnosis was retained after the first consultation, they were offered participation in the study and informed consent was obtained. An influenza-like illness was defined as **documented fever of ≥38 °C or anamnestic fever, plus cough or sore throat.** An international trip was defined as a journey to any destination except to the neighboring countries of Switzerland (Germany, France, Italy, Austria, and Liechtenstein).

After clinical assessment, the attending physician was asked to estimate the probability of influenza and to evaluate the general condition of the patient on a scale from 1 to 10 (1 very bad general condition, 10 = general condition as usual). A single naso-pharyngeal swab was taken and put in 3 ml of Copan universal transport medium (Copan Diagnostics Inc., Corona, CA, USA). Patients were then randomly assigned to have an iRDT or not. The attending physician called one of the investigators (SV), who flipped a coin to decide whether an iRDT had to be done or not. For the patients who were allocated to have an iRDT, 300 μl of the above-mentioned solution was used to perform a BD Directigen™ Flu A + B rapid test (Becton and Dickinson, Maryland, USA) according to the manufacturer's instructions. The results of the iRDT were available to the attending physician for further medical management. The rest of the solution was stored at −20 °C. A real-time PCR for influenza was done in batches at the end of the study