Ensuring the Safety of Yellow Fever Vaccination in Travelers—The Experience at a Large U.S. Academic Medical Center in Colorado

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Abstract: Background: Yellow fever (YF) virus has the potential to cause fatal outcomes among at-risk individuals visiting endemic areas. Vaccinating travelers who are at risk is necessary to prevent virus-related life-threatening complications. We lack data on the clinical features of persons seeking YF vaccination. We aim to describe the characteristics of a cohort of persons receiving the YF vaccine before travel. Methods: A retrospective analysis of 964 travelers receiving the YF vaccine (Stamaril®) from Oct 2016 to Jul 2019 was performed at the University of Colorado Hospital, U.S. Percentages, means, and standard deviations were calculated. A multivariate logistic regression model was built to evaluate the association between receiving YF vaccination less than 10 days before departure and visiting friends and relatives (VFR). Results: The average age of the subjects was 39 ± 18 years with a range of nine months to 83 years. Persons who were 60 years of age and older represented 17%. Women consisted of 52%, and most of the travelers were Caucasians (64%). Travelers reported traveling to Africa (57%) or South America (40%). The primary destinations for travelers overall were Kenya (19%), Uganda (11%), and Tanzania (11%) in Africa; and Peru (14%) and Brazil (13%) in South America. The most common reasons for travel included leisure (44%), VFR (18%), and mission trips (10%). Comorbidities included a history of hematologic disorders (4%), HIV infection (2%), and diabetes mellitus (3%). The average duration between vaccine administration and travel was 43 days. Those VFR were two times more likely to receive the YF vaccination <10 days before departure. Conclusions: Identifying the type of travel, itinerary, and underlying medical conditions allows providers to administer the YF vaccine to travelers safely. There is a need to identify strategies to improve the timing of YF vaccination among VFR travelers.

Keywords: yellow fever virus; yellow fever vaccine; travel medicine; health policy
1. Introduction

Yellow fever (YF) is a hemorrhagic disease caused by a flavivirus and transmitted by the *Aedes aegypti* mosquito, which is found in parts of tropical South America and sub-Saharan Africa. Since the early 1990s, the World Health Organization (WHO) estimates that there have been 200,000 cases of YF and 30,000 deaths due to the disease worldwide [1]. An analysis of African data sources in 2013 estimated that the burden of YF was 130,000 severe cases and 78,000 deaths [2].

Treatment for patients with YF is mainly supportive, as there is no specific antiviral therapy available. However, the YF vaccine is widely used for the prevention of YF in travelers, and for people living in endemic areas. There are 20–60 million doses of the vaccine distributed annually [3]. YF-VAX® and Stamaril® are live attenuated vaccines prepared by culturing the 17D-204 strain of the virus in chicken embryos, and their efficacy is based upon the development of neutralizing antibodies [4]. The vaccine has been used since the 1930s when it was first developed. WHO modified the length of validation by the vaccine in 2016 from 10 years to lifelong duration for most individuals [5]. In the U.S., the YF vaccine is primarily given as prophylaxis to military personnel and patients at risk due to travel to endemic areas. Sanofi held the manufacturing of YF-VAX® in 2016 due to factory production issues, and the company made available an alternative vaccine, Stamaril®, which is administered in the U.S. through an FDA-approved expanded access program. Standard clinical practice of screening patients during the pre-travel encounter is essential to prevent complications associated with YF vaccination. YF is a live attenuated vaccine with known serious adverse events, including vaccine-associated viscerotropic disease (YEL-AVD) and neurotropic disease (YEL-AND). Risk factors include uncontrolled HIV infection, 60 years and older patients [6], and other immunocompromised conditions. The subgroup of patients traveling to visit friends and relatives (VFR) can be a particularly vulnerable population at higher risk for some preventable infections, such as malaria, due to loss of previous immunity, and a lesser likelihood to seek pre-travel advice or take prophylaxis, while going back to their home countries [7,8]. There are limited studies in the U.S. that describe the patient population receiving the YF vaccine. This study aimed to identify important descriptors of patients getting the YF vaccine before travel, including patients traveling to visit friends and relatives. This information can aid public health agencies to enhance strategies to increase immunizations of patients at risk and avoid complications.

2. Methods

2.1. Ethics Statement

The present investigation complies with the Health Insurance Portability and Accountability Act (HIPAA) according to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado Denver. Patients received the YF vaccine through an approved Sanofi Pasteur Inc. Protocol Number STA00011, Expanded Access IND Program to Provide Stamaril® YF Vaccine (17D-204 strain) to Persons in the United States (Quorum Review File #32032). Analysis of clinical data has been performed under an approved protocol (COMIRB Protocol 17-1032).

2.2. Patients and Data Collection

Data from patients receiving the Stamaril® vaccine at the University of Colorado Hospital clinic from 31 October 2016 to 7 July 2019, were submitted for data extraction. Electronic medical records (EPIC) were automatically interrogated for the cohort of travelers through a software supported by Health Data Compass Data Warehouse project (healthdatacompass.org). Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado Denver. The following variables were automatically collected: gender, age, race, state of residency, date of YF vaccine, and the following comorbidities based on International Classification of Diseases (ICD) codes: diabetes mellitus, neoplasms, HIV infection, history of hematology-immune disorders, and pregnancy (see Appendix A for full ICD-9, and ICD-10 code definitions). VFR was defined as a form of travel
wherein the purpose of the trip or the type of accommodation was visiting friends and/or relatives as consigned in the patient’s history. The following variables were manually collected through chart review: verification of vaccine date if it was unavailable per the automatic search, pregnancy at the time of vaccine administration, the reason for travel, the continent of travel, and destination countries. Some travelers had missing information on key variables (Table 1).

Table 1. A cohort of travelers receiving the yellow fever vaccine at the University of Colorado Hospital.

| Variables                              | Total (n = 964) | Visit F&R, N = 170 (18%) | Other Reason, N = 794 (82%) | p-Value |
|----------------------------------------|-----------------|--------------------------|-----------------------------|---------|
| Age (years), mean (SD)                 | 39 (18)         | 30 (20)                  | 41 (17)                     | <0.0001 |
| Age ≥ 60 years old                    | 167 (17%)       | 18 (11%)                 | 149 (19%)                   | 0.01    |
| Sex, female                           | 502 (52%)       | 74 (44%)                 | 428 (54%)                   | 0.01    |
| Race                                   |                 |                          |                             |         |
| African American                      | 614 (64%)       | 36 (21%)                 | 578 (73%)                   | <0.0001 |
| Other                                  | 142 (15%)       | 104 (61%)                | 38 (5%)                     |         |
| Out of Colorado State                 | 208 (22%)       | 30 (18%)                 | 178 (22%)                   |         |
| Pregnancy                              | 11 (2%)         | 5 (3%)                   | 6 (1%)                      | 0.004   |
| Hematologic/Immunologic Disease       | 36 (4%)         | 9 (5%)                   | 27 (3%)                     | 0.237   |
| Diabetes Mellitus                     | 27 (3%)         | 6 (4%)                   | 21 (3%)                     | 0.526   |
| Neoplasm                               | 72 (7%)         | 7 (4%)                   | 65 (8%)                     | 0.07    |
| HIV                                    | 22 (2%)         | 12 (7%)                  | 10 (1%)                     | <0.0001 |
| Destination                            |                 |                          |                             |         |
| Africa                                 | 551 (57%)       | 146 (86%)                | 405 (51%)                   | <0.0001 |
| South America                          | 387 (40%)       | 22 (13%)                 | 365 (46%)                   |         |
| Other                                  | 26 (3%)         | 2 (1%)                   | 24 (3%)                     |         |
| Time between vaccine administration and departure (days), mean (SD) | 41 (38) | 34 (39) | 43 (38) | 0.0049 |
| Vaccination < 10 days                  | 110 (11%)       | 30 (18%)                 | 80 (10%)                    | 0.005   |

2.3. Statistical Analysis

The means and standard deviations for continuous variables were calculated. For categorical variables, frequencies and percentages were calculated. Patient characteristics were compared between those reporting to visit friends and relatives versus other reasons of travel using chi-squared, students t-tests, or Fisher exact tests. A multivariate logistic regression model was built to evaluate the association between those receiving YF vaccination less than 10 days before departure and those VFR, after controlling for confounders of age, sex, race, and the continent of travel. All analyses were conducted in SAS 9.4. We selected the 10 days based on WHO recommendation of the optimal time of immunization against YF before traveling to endemic areas [9].

Data access: The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

3. Results

3.1. Clinical Characteristics of Patients Receiving the Yellow Fever Vaccine:

Of 964 subjects, the average age of travelers receiving the vaccine was 39 years with a range from nine months to 83 years (Table 1). There were more females (52%), and most of the travelers were identified as Caucasian (64%). Most travelers were from the State of Colorado (96%). Travelers predominantly reported travel to Africa (57%) or South America (40%), among which the primary destinations included Kenya (19%), Uganda (11%), and Tanzania (11%) in Africa; and Peru (14%) and Brazil (13%) in South America (Figure 1). The most common reasons for travel included leisure (44%), followed by VFR (18%) and mission trips (10%) (Figure 2). Comorbidities were uncommon but included a history of neoplasm (7%), hematologic/immunologic disorders (4%), HIV infection...
(2%), and diabetes mellitus (3%). Heme/immune diagnosis captured through ICD codes included benign heme disorders such as polycythemia, pancytopenia, sickle cell trait, thalassemia, history of deep venous thrombosis, previous use of systemic lupus erythematosus medications, and unspecified immune disorders (Appendix A). Common ICD neoplasm diagnoses captured were benign tumors of the skin, prostate, and uterus; and history of colorectal cancer, melanoma, multiple myeloma, uterus carcinoma, kidney cancer, bladder cancer, and others (Appendix A). The average duration between vaccine administration and travel was 43 days. No evidence of mild or life-threatening reactions to Stamaril® occurred in this large cohort.

Figure 1. Heat map of destinations among patients receiving the yellow fever (YF) vaccine. (A). Heat map of countries of destination for the total cohort. (B). Heat map for travelers going for leisure. (C). Heat map for travelers going to visit friends and family. The density of patients is represented by color bars.
Travelers who were 60 years of age and older represented 17% of the total study population. They were 53% women, predominantly white (79%), and mostly traveling for leisure (63%). They visited Africa (52%) and South America (47%) more often and had plenty of time to receive the vaccine before departure with a mean of 50 days. Kenya (23%), Tanzania (22%), Brazil (24%), and Peru (16%) were popular destinations among these travelers. Only 7% received the vaccine less than 10 days from departure. Sixty years or older travelers had higher rates of heme-immune conditions (8%), diabetes mellitus (8%), and neoplasms (22%).

Since the vaccine is licensed only to infants older than nine months of age, we only had four infants less than one year of age in our cohort, representing 0.4%. We did not have any reported side effects or complications in this group of travelers.

### 3.2. Travelers Visiting Friends and Relatives

Travelers visiting their friends and relatives were more predominantly men (56%), younger, and identified as African Americans for their primary ethnicity. Women in this subgroup were more likely to be pregnant and more likely to be HIV positive, but less likely to have a history of cancer. They were more likely to visit Africa as opposed to South America, and they had less time between vaccine administration and travel departure. Common destinations were Kenya, Ethiopia, and less commonly Brazil (Figure 1C). VFR travelers were more likely to receive the vaccine less than 10 days before departure compared to other reasons for travel (18% vs. 10%, \( p = 0.005 \)). Those VFR were 2.2 times \((OR 2.2 (1.3–3.7), p = 0.003)\) more likely to receive the YF vaccination <10 days before departure, after controlling for confounders of age, sex, race, and destination of Africa vs. South America.

### 4. Discussion

We describe the clinical characteristics of a cohort of travelers seeking YF vaccination at a U.S medical center. Some of those travelers presented themselves as family groups. Most were young adults, but the age varied widely from infants to seniors. In Colorado, most travelers were Caucasian,
had a few comorbidities, and traveled to Africa most often. Travelers sought YF vaccination on an average of about a month and a half before their departure date. The subgroup of VFR travelers was younger, of African American descent, traveling to the African continent, more often pregnant, and had a higher likelihood of having an HIV infection.

We also showed that VFR travelers were more likely to receive the YF vaccine at a suboptimal time before travel. WHO recommends immunization against YF at least 10 days before travel to endemic areas [9]. Studies in travel clinics have shown inadequate timing of the YF vaccine before travel in children [10]. Those VFR may have a harder time making travel clinic appointments and may present just before travel and may be less prepared to take appropriate preventative measures [11].

Receiving the vaccine less than 10 days prior can also have implications for possible denial of entry or increased paperwork at the country of destination. Those VFR may also not recognize the specific country requirement of YF vaccination until just shortly before departure. VFR travelers carry a higher risk of acquired travel-related illnesses such as Hepatitis A, typhoid, malaria, soil-transmitted helminths, and influenza [12]. Specific risk factors associated with the increased threat of illness among VFR include longer stays, decreased pre-travel health plans, sick contacts while abroad, and poorer sanitary conditions during their stay. Public health interventions can aim to increase rates and enhance the optimal timing of YF vaccination among those VFR.

We have shown a large cohort of travelers who safely received the YF vaccine before travel. Since the rate of adverse events with the Yellow vaccine is of about three events per 100,000 doses [13], with our relatively small representative sample we cannot extrapolate a different safety profile. Nevertheless, through standardized travel advice encounters, we safely delivered the vaccine to more than 150 travelers aged 60 years or older, travelers with controlled HIV, and history of cancer, pregnancy, or heme-immune disorders not listed as absolute contraindications. Although travel clinic providers screened travelers for contraindications to receive the YF vaccine, the more comprehensive interrogation of our electronic medical records found a small rate of non-prohibitive relative contraindications in some travelers. We still encourage the avoidance of vaccination in travelers with relative contraindications if the risk of YF acquisition during travel is deemed low, but our findings suggest vaccination is safe in this relatively small cohort among travelers older than 60 years of age. Our cohort delivered some safety evidence of YF vaccine administration among travelers with those listed conditions. This data can reassure clinicians and travelers with a history of those conditions to make pre-travel decisions where the YF vaccine administration is mandatory.

Previous reports in Nigeria have documented the safe administration of the YF vaccine during pregnancy [14]. Administration of the vaccine to HIV-infected individuals with CD4 counts greater than 500 cells/mm$^3$ is safe [15]. YF vaccine has been also administered safely in immunocompromised patients after the withdrawal of their immunosuppressive therapy [16,17].

Our population of travelers visiting family and friends reflects the diversity of African immigrants in Aurora, Colorado. A significant number of travelers seeking pre-travel advice will benefit from a continued comprehensive pre-travel screening of immunocompromised conditions.

Providing the YF vaccine remains a critical public health strategy to decrease transmission and disease. Although overall coverage for the YF vaccine has increased in endemic countries [18], travelers are an important target for this preventive strategy as well. Data from the recent Brazilian outbreak found a case fatality of up to 40% among unimmunized travelers [19].

Models incorporating clinical features have been important to showcase disease burden and to enhance vaccination strategies [20]. The study of high-risk populations can inform the best vaccine policies [21]. VFR travelers are considered a high-risk population. We recommend public health policies to enhance the inclusion of vulnerable populations such as people VFR for YF prophylaxis. We should explore policies such as outreach community messages on the importance of pre-travel health care among foreign-born populations in the US. Additional considerations include community health workers reaching VFR communities to explain the importance of pre-travel vaccination and assessing individual risks.
There are a few limitations to this study. The retrospective selection of data limits the reliability and number of variables analyzed. Misdiagnosis or irrelevant past medical history could have been selected through the automatic ICD screening of the previous diagnosis. However, selection bias was decreased through the automatic collection of some key risk factor variables. Missing data occurred in some medical records as well. We did not have data on foreign-born status among the VFR travelers, which can also account for different clinical characteristics or outcomes.

YF vaccine remains a priority for decreasing disease burden. Coloradans seeking the vaccine represent the current demographics of our community. Despite the history of uncommon well-known comorbidities, YF vaccination was effective and safe. YF disease remains a potentially lethal complication during travel. The current outbreak in Nigeria and the 2018 outbreak in Brazil, both with high case fatality ratios, highlight that prevention strategies are a priority. Efforts should be enhanced to continue YF disease prevention strategies in travel clinics throughout the United States.

Author Contributions: M.B. performed data collection and helped in drafting the first version of the manuscript. J.S. provided critical edits to the manuscript and assisted with the statistical analysis. K.T., D.M., and E.R. assisted with data collection and provided edits to the manuscript. S.A., S.C., W.M., D.C., and C.F.-P. provided critical edits to the manuscript. A.F.H.-M. had the original research idea, assisted with data collection, helped to draft the manuscript, and assisted with data analysis. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: A.H.M. was the recipient of a K12-clinical trial award as a co-principal investigator for the Expanded Access IND Program (EAP) to provide Stamaril Vaccine to Persons in the United States for Vaccination against Yellow Fever. The rest of the authors declare no conflict of interest.

Appendix A

Table A1. List of diagnoses by ICD codes in yellow fever recipients, University of Colorado Hospital, Denver, 2016–2019.

| ICD    | ICD-Code | Diagnosis                                                                 | Categories |
|--------|----------|---------------------------------------------------------------------------|------------|
| ICD-9-CM | 250.8    | Xanthoma diabeticorum                                                    | DM         |
| ICD-9-CM | 250.6    | Well controlled type 2 diabetes mellitus with peripheral neuropathy (HC code) | DM         |
| ICD-9-CM | 250.7    | Well controlled type 2 diabetes mellitus with peripheral circulatory disorder (HC code) | DM         |
| ICD-9-CM | 250      | Well controlled type 2 diabetes mellitus (HC code)                        | DM         |
| ICD-9-CM | 250.61   | Well controlled type 1 diabetes mellitus with peripheral neuropathy (HC code) | DM         |
| ICD-9-CM | 250.01   | Well controlled type 1 diabetes mellitus (HC code)                        | DM         |
| ICD-9-CM | 250.5    | Visual loss due to diabetes mellitus (HC code)                            | DM         |
| ICD-9-CM | 250.9    | Unspecified diabetes mellitus with unspecified complications             | DM         |
| ICD-9-CM | 250.02   | Uncontrolled type II diabetes mellitus with nephropathy                   | DM         |
| ICD-9-CM | 250.92   | Uncontrolled type 2 diabetes mellitus with complication (HC code)         | DM         |
| ICD-9-CM | 249.6    | Ulnar neuropathy due to secondary DM (HC code)                            | DM         |
| ICD-9-CM | 250.81   | Type I diabetes with complications                                       | DM         |
| ICD-10-CM | E11.9    | Type 2 diabetes mellitus without complications                            | DM         |
| ICD-10-CM | ICD-Code | Diagnosis                                                                 | Categories |
|-----------|----------|---------------------------------------------------------------------------|------------|
| E11.311   | Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema | DM         |
| E11.8     | Type 2 diabetes mellitus with unspecified complications                     | DM         |
| E11.69    | Type 2 diabetes mellitus with other specified complication                   | DM         |
| E11.39    | Type 2 diabetes mellitus with other diabetic ophthalmic complication        | DM         |
| E11.49    | Type 2 diabetes mellitus with other diabetic neurological complication       | DM         |
| E11.59    | Type 2 diabetes mellitus with other circulatory complications               | DM         |
| E11.3393  | Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral | DM         |
| E11.3293  | Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral | DM         |
| E11.3219  | Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye | DM         |
| E11.649   | Type 2 diabetes mellitus with hypoglycemia without coma                     | DM         |
| E11.65    | Type 2 diabetes mellitus with hyperglycemia                                 | DM         |
| E11.621   | Type 2 diabetes mellitus with foot ulcer                                    | DM         |
| E11.42    | Type 2 diabetes mellitus with diabetic polyneuropathy                       | DM         |
| E11.40    | Type 2 diabetes mellitus with diabetic neuropathy, unsp                     | DM         |
| E11.610   | Type 2 diabetes mellitus with diabetic neuropathic arthropathy             | DM         |
| E11.43    | Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy          | DM         |
| E11.44    | Type 2 diabetes mellitus with diabetic amyotrophy                           | DM         |
| E11.3299  | Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified | DM         |
| E10.9     | Type 1 diabetes mellitus without complications                             | DM         |
| E10.649   | Type 1 diabetes mellitus with hypoglycemia without coma                    | DM         |
| E10.65    | Type 1 diabetes mellitus with hyperglycemia                                | DM         |
| E13.44    | Other specified diabetes mellitus with diabetic amyotrophy                 | DM         |
| 359.1     | Wielander’s distal dystrophy (HC code)                                     | Heme/Immune|
| 287.2     | Vasculitis, hemorrhagic                                                    | Heme/Immune|
| 287.5     | Unspecified thrombocytopenia                                                | Heme/Immune|
| 279.3     | Unspecified immunity deficiency                                             | Heme/Immune|
| 287.9     | Unspecified hemorrhagic conditions                                          | Heme/Immune|
| 279.9     | Unspecified disorder of immune mechanism                                   | Heme/Immune|
| 795.09    | Unexplained endometrial cells on cervical Pap smear                         | Heme/Immune|
| 795.51    | Tuberculin test reaction                                                   | Heme/Immune|
| D69.6     | Thrombocytopenia, unspecified                                              | Heme/Immune|
| D56.3     | Thalassemia minor                                                          | Heme/Immune|
| 795.79    | Systemic lupus erythematosus inhibitor (HC code)                            | Heme/Immune|
| 203       | Stage III multiple myeloma (HC code)                                       | Neoplasms  |
| D57.3     | Sickle-cell trait                                                         | Heme/Immune|
| D75.1     | Secondary polycythemia                                                     | Heme/Immune|
| D86.3     | Sarcoidosis of skin                                                        | Heme/Immune|
| 795.52    | Response to cell-mediated gamma interferon antigen without active tuberculosis | Heme/Immune|
Table A1. Cont.

| ICD       | ICD-Code | Diagnosis                                                                 | Categories               |
|-----------|----------|---------------------------------------------------------------------------|--------------------------|
| ICD-10-CM | D69.1    | Qualitative platelet defects                                               | Heme/Immune              |
| ICD-10-CM | D68.52   | Prothrombin gene mutation                                                 | Heme/Immune              |
| ICD-9-CM  | 279.49   | Progesterone dermatitis                                                   | Heme/Immune              |
| ICD-10-CM | 795.05   | Positive cervical papilloma DNA test                                      | Neoplasms                |
| ICD-10-CM | Z86.73   | Personal history of transient ischemic attack (TIA), and cerebral          | Heme/Immune              |
|           |          | infarction without residual deficits                                       |                          |
| ICD-10-CM | Z86.711  | Personal history of pulmonary embolism                                    | Heme/Immune              |
| ICD-10-CM | Z86.718  | Personal history of other venous thrombosis and embolism                   | Heme/Immune              |
| ICD-10-CM | Z86.59   | Personal history of other mental and behavioral disorders                  | Heme/Immune              |
| ICD-10-CM | Z92.89   | Personal history of other medical treatment                                | Heme/Immune              |
| ICD-10-CM | Z86.19   | Personal history of other infectious and parasitic diseases                | Heme/Immune              |
| ICD-10-CM | Z86.69   | Personal history of other diseases of the nervous system and sense organs | Heme/Immune              |
| ICD-10-CM | Z86.79   | Personal history of other diseases of the circulatory system               | Heme/Immune              |
| ICD-10-CM | Z86.018  | Personal history of other benign neoplasm                                  | Neoplasms                |
| ICD-10-CM | Z86.13   | Personal history of malaria                                                | Heme/Immune              |
| ICD-10-CM | Z86.008  | Personal history of in-situ neoplasm of other site                         | Heme/Immune              |
| ICD-10-CM | Z86.39   | Personal history of endo, nutritional and metabolic disease                | Heme/Immune              |
| ICD-10-CM | Z86.2    | Personal history of diseases of the blood and blood-forming organs and     | Heme/Immune              |
|           |          | certain disorders involving the immune mechanism                           |                          |
| ICD-10-CM | Z86.010  | Personal history of colonic polyps                                         | Heme/Immune              |
| ICD-10-CM | Z92.21   | Personal history of antineoplastic chemotherapy                            | Heme/Immune              |
| ICD-9-CM  | 795.03   | Papanicolaou smear of cervix with low grade squamous intraepithelial       | Heme/Immune              |
|           |          | lesion (LGSIL)                                                             |                          |
| ICD-9-CM  | 795.01   | Papanicolaou smear of cervix with atypical squamous cells of undetermined  | Heme/Immune              |
|           |          | significance (ASC-US)                                                     |                          |
| ICD-10-CM | D89.89   | Other specified disorders involving the immune mechanism, not              | Heme/Immune              |
|           |          | elsewhere classified                                                       |                          |
| ICD-10-CM | D64.89   | Other specified anemias                                                    | Heme/Immune              |
| ICD-10-CM | D68.59   | Other primary thrombophilia                                                | Heme/Immune              |
| ICD-10-CM | D61.818  | Other pancytopenia                                                         | Heme/Immune              |
| ICD-10-CM | D69.2    | Other nonthrombocytopenic purpura                                          | Heme/Immune              |
| ICD-10-CM | D50.8    | Other iron deficiency anemias                                              | Heme/Immune              |
| ICD-10-CM | D70.9    | Neutropenia, unspecified                                                   | Heme/Immune              |
| ICD-10-CM | D70.3    | Neutropenia due to infection                                               | Heme/Immune              |
| ICD-10-CM | D50.9    | Iron deficiency anemia, unspecified                                        | Heme/Immune              |
| ICD-10-CM | D50.0    | Iron deficiency anemia secondary to blood loss (chronic)                   | Heme/Immune              |
| ICD-10-CM | D84.9    | Immunodeficiency, unspecified                                              | Heme/Immune              |
| ICD-10-CM | D89.42   | Idiopathic mast cell activation syndrome                                  | Heme/Immune              |
| ICD-10-CM | D69.9    | Hemorrhagic condition, unspecified                                         | Heme/Immune              |
| ICD-10-CM | D72.0    | Genetic anomalies of leukocytes                                            | Heme/Immune              |
| ICD-10-CM | Z51.81   | Encounter for therapeutic drug level monitoring                            | Heme/Immune              |
| ICD-10-CM | Z51.5    | Encounter for palliative care                                              | Heme/Immune              |
| ICD-10-CM | Z51.89   | Encounter for other specified aftercare                                    | Heme/Immune              |
| ICD-10-CM | Z51.12   | Encounter for antineoplastic immunotherapy                                | Heme/Immune              |
Table A1. Cont.

| ICD-10-CM | ICD-Code | Diagnosis                                      | Categories          |
|-----------|----------|-----------------------------------------------|---------------------|
| ICD-10-CM | Z51.11   | Encounter for antineoplastic chemotherapy     | Heme/Immune         |
| ICD-10-CM | D72.829  | Elevated white blood cell count, unspecified  | Heme/Immune         |
| ICD-10-CM | D72.9    | Disorder of white blood cells, unspecified    | Heme/Immune         |
| ICD-10-CM | D89.9    | Disorder involving the immune mechanism, unspecified | Heme/Immune         |
| ICD-10-CM | D75.9    | Disease of blood and blood-forming organs, unspecified | Heme/Immune         |
| ICD-10-CM | D72.819  | Decreased white blood cell count, unspecified | Heme/Immune         |
| ICD-10-CM | D68.9    | Coagulation defect, unspecified               | Heme/Immune         |
| ICD-10-CM | D64.9    | Anemia, unspecified                           | Heme/Immune         |
| ICD-10-CM | D68.51   | Activated protein C resistance                | Heme/Immune         |
| ICD-9-CM  | V65.5    | Worried well                                  | HIV                 |
| ICD-9-CM  | V65.3    | Weight loss, intentional                     | HIV                 |
| ICD-9-CM  | V65.40   | Visit for counseling                          | HIV                 |
| ICD-9-CM  | V08      | Viruses, lymphadenopathy-associated           | HIV                 |
| ICD-9-CM  | V65.49   | Surgical counseling visit                     | HIV                 |
| ICD-9-CM  | V65.8    | Reasons for seeking consultation              | HIV                 |
| ICD-10-CM | B20      | Human immunodeficiency virus (HIV) disease    | HIV                 |
| ICD-9-CM  | V65.41   | Exercise counseling                           | HIV                 |
| ICD-10-CM | Z21      | Asymptomatic human immunodeficiency virus infection status | HIV                 |
| ICD-9-CM  | 186.9    | Yolk Sac Tumour                               | Neoplasms           |
| ICD-9-CM  | 193      | Wucherde struma langhans                     | Neoplasms           |
| ICD-9-CM  | 189      | WT (Wilms tumor) (HC code)                    | Neoplasms           |
| ICD-9-CM  | 210.2    | Warthin’s tumour                              | Neoplasms           |
| ICD-10-CM | C88.0    | Waldenstrom macroglobulinemia                | Neoplasms           |
| ICD-9-CM  | 184.4    | Vulvar malignant neoplasm (HC code)           | Neoplasms           |
| ICD-9-CM  | 182      | Uterus neoplasms                              | Neoplasms           |
| ICD-9-CM  | 188.9    | Urinary bladder cancer (HC code)              | Neoplasms           |
| ICD-10-CM | C44.90   | Unspecified malignant neoplasm of skin, unspecified | Neoplasms           |
| ICD-9-CM  | 173.9    | Unspecified malignant neoplasm of skin, site unspecified | Neoplasms           |
| ICD-10-CM | C44.40   | Unspecified malignant neoplasm of skin of scalp and neck | Neoplasms           |
| ICD-9-CM  | 173.4    | Unspecified malignant neoplasm of scalp and skin of neck | Neoplasms           |
| ICD-9-CM  | 201.9    | Unspecified Hodgkin’s disease, site unspecified, extranodal and solid organ sites | Neoplasms           |
| ICD-9-CM  | 162.9    | Undifferentiated carcinoma of lung (HC code)  | Neoplasms           |
| ICD-9-CM  | 173.91   | Ulcers, rodent                                | Neoplasms           |
| ICD-9-CM  | 174.9    | Tubular carcinoma of breast (HC code)         | Neoplasms           |
| ICD-9-CM  | 185      | Transitional cell carcinoma of prostate (HC code) | Neoplasms           |
| ICD-9-CM  | 145.9    | The mouth cancers                             | Neoplasms           |
| ICD-9-CM  | 162.3    | Syndromes, Pancoast’s                         | Neoplasms           |
| ICD-9-CM  | 173.99   | Sweat gland tumor, malignant                  | Neoplasms           |
| ICD-9-CM  | 172.9    | Superficial spreading melanoma (HC code)      | Neoplasms           |
| ICD-10-CM | D25.2    | Subserosal leiomyoma of uterus                | Neoplasms           |
| ICD-9-CM  | 154.1    | Stage IV carcinoma of rectum (HC code)        | Neoplasms           |
| ICD-9-CM  | 210.4    | Squamous papilloma of uvula                   | Neoplasms           |
| ICD-9-CM  | 173.62   | Squamous cell skin cancer, wrist              | Neoplasms           |
| ICD-9-CM  | 173.42   | Squamous cell skin cancer, parietal           | Neoplasms           |
Table A1. Cont.

| ICD   | ICD-Code  | Diagnosis                                      | Categories    |
|-------|-----------|-----------------------------------------------|---------------|
| ICD-9-CM | 173.92    | Squamous cell skin cancer                      | Neoplasms     |
| ICD-9-CM | 173.9     | Squamous Cell Epithelioma                      | Neoplasms     |
| ICD-10-CM | C44.92    | Squamous cell carcinoma of skin, unspecified  | Neoplasms     |
| ICD-10-CM | C44.42    | Squamous cell carcinoma of skin of scalp and neck | Neoplasms     |
| ICD-10-CM | C44.622   | Squamous cell carcinoma of skin of right upper limb, including shoulder | Neoplasms     |
| ICD-10-CM | C44.329   | Squamous cell carcinoma of skin of other parts of face | Neoplasms     |
| ICD-10-CM | C44.321   | Squamous cell carcinoma of skin of nose        | Neoplasms     |
| ICD-9-CM | 154.3     | Squamous cell carcinoma of anus (HC code)      | Neoplasms     |
| ICD-9-CM | 173.41    | Skin cancer of scalp or skin of neck           | Neoplasms     |
| ICD-9-CM | 173.31    | Skin cancer of nose                            | Neoplasms     |
| ICD-9-CM | 173.51    | Skin cancer of anterior chest                  | Neoplasms     |
| ICD-9-CM | 197       | Secondary teratoma of lung (HC code)           | Neoplasms     |
| ICD-10-CM | C78.00    | Secondary malignant neoplasm of unspecified lung | Neoplasms     |
| ICD-10-CM | C78.01    | Secondary malignant neoplasm of right lung     | Neoplasms     |
| ICD-10-CM | C78.02    | Secondary malignant neoplasm of left lung      | Neoplasms     |
| ICD-9-CM | 154       | Recurrent squamous cell carcinoma of colorectal region (HC code) | Neoplasms     |
| ICD-9-CM | 173.61    | Recurrent basal cell carcinoma of shoulder      | Neoplasms     |
| ICD-9-CM | 174.2     | Primary malignant neoplasm of upper inner quadrant of female breast (HC code) | Neoplasms     |
| ICD-10-CM | C44.99    | Other specified malignant neoplasm of skin, unspecified | Neoplasms     |
| ICD-10-CM | D26.9     | Other benign neoplasm of uterus, unspecified  | Neoplasms     |
| ICD-10-CM | D23.9     | Other benign neoplasm of skin, unspecified     | Neoplasms     |
| ICD-10-CM | D23.60    | Other benign neoplasm of skin of unspecified upper limb, including shoulder | Neoplasms     |
| ICD-10-CM | D23.30    | Other benign neoplasm of skin of unspecified part of face | Neoplasms     |
| ICD-10-CM | D23.70    | Other benign neoplasm of skin of unspecified lower limb, including hip | Neoplasms     |
| ICD-10-CM | D23.5     | Other benign neoplasm of skin of trunk         | Neoplasms     |
| ICD-10-CM | D23.4     | Other benign neoplasm of skin of scalp and neck | Neoplasms     |
| ICD-10-CM | D23.71    | Other benign neoplasm of skin of right lower limb, including hip | Neoplasms     |
| ICD-10-CM | D23.62    | Other benign neoplasm of skin of left upper limb, including shoulder | Neoplasms     |
| ICD-9-CM | 210       | Neurofibroma of lip                            | Neoplasms     |
| ICD-10-CM | D49.89    | Neoplasm of unspecified behavior of other specified sites | Neoplasms     |
| ICD-10-CM | D49.7     | Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system | Neoplasms     |
| ICD-10-CM | D49.0     | Neoplasm of unspecified behavior of digestive system | Neoplasms     |
| ICD-10-CM | D49.2     | Neoplasm of unspecified behavior of bone, soft tissue, and skin | Neoplasms     |
| ICD-10-CM | D48.9     | Neoplasm of uncertain behavior, unspecified    | Neoplasms     |
| ICD-10-CM | D48.5     | Neoplasm of uncertain behavior of skin         | Neoplasms     |
| ICD-9-CM | 172.6     | Nail bed melanoma, upper extremity (HC code)  | Neoplasms     |
| ICD-10-CM | C90.00    | Multiple myeloma not having achieved remission | Neoplasms     |
| ICD-10-CM | D47.2     | Monoclonal gammopathy                          | Neoplasms     |
| ICD-9-CM | 172.5     | Melanoma, skin of trunk                        | Neoplasms     |
| ICD-9-CM | 172.7     | Melanoma, skin of lower limb                   | Neoplasms     |
| ICD-10-CM | D03.4     | Melanoma in situ of scalp and neck             | Neoplasms     |
| ICD-10-CM | D03.59    | Melanoma in situ of other part of trunk        | Neoplasms     |
| ICD-10-CM | D03.62    | Melanoma in situ of left upper limb, including shoulder | Neoplasms     |
| ICD      | ICD-Code | Diagnosis                                      | Categories         |
|----------|----------|-----------------------------------------------|--------------------|
| ICD-10-CM | D22.9    | Melanocytic nevi, unspecified                 | Neoplasms          |
| ICD-10-CM | D22.70   | Melanocytic nevi of unspecified lower limb, including hip | Neoplasms          |
| ICD-10-CM | D22.60   | Melanocytic nevi of unsp upper limb, including shoulder | Neoplasms          |
| ICD-10-CM | D22.5    | Melanocytic nevi of trunk                     | Neoplasms          |
| ICD-10-CM | D22.4    | Melanocytic nevi of scalp and neck            | Neoplasms          |
| ICD-10-CM | D22.61   | Melanocytic nevi of right upper limb, including shoulder | Neoplasms          |
| ICD-10-CM | D22.71   | Melanocytic nevi of right lower limb, including hip | Neoplasms          |
| ICD-10-CM | D22.39   | Melanocytic nevi of other parts of face       | Neoplasms          |
| ICD-10-CM | D22.62   | Melanocytic nevi of left upper limb, including shoulder | Neoplasms          |
| ICD-10-CM | D22.72   | Melanocytic nevi of left lower limb, including hip | Neoplasms          |
| ICD-10-CM | C51.9    | Malignant neoplasm of vulva, unspecified      | Neoplasms          |
| ICD-10-CM | C55      | Malignant neoplasm of uterus, part unspecified | Neoplasms          |
| ICD-9-CM  | 174.4    | Malignant neoplasm of upper-inner quadrant of right female breast (HC code) | Neoplasms          |
| ICD-10-CM | C50.412  | Malignant neoplasm of upper-quadrant of left female breast | Neoplasms          |
| ICD-10-CM | C50.211  | Malignant neoplasm of upper-inner quadrant of right female breast | Neoplasms          |
| ICD-10-CM | C34.12   | Malignant neoplasm of lower lobe, left bronchus or lung | Neoplasms          |
| ICD-10-CM | C50.919  | Malignant neoplasm of unspecified site of unspecified female breast | Neoplasms          |
| ICD-10-CM | C50.912  | Malignant neoplasm of unspecified site of left female breast | Neoplasms          |
| ICD-10-CM | C34.90   | Malignant neoplasm of unspecified part of unspecified bronchus or lung | Neoplasms          |
| ICD-10-CM | C34.92   | Malignant neoplasm of unspecified part of left bronchus or lung | Neoplasms          |
| ICD-10-CM | C64.9    | Malignant neoplasm of unspecified kidney, except renal pelvis | Neoplasms          |
| ICD-10-CM | C50.911  | Malignant neoplasm of unsp site of right female breast | Neoplasms          |
| ICD-10-CM | C73      | Malignant neoplasm of thyroid gland           | Neoplasms          |
| ICD-10-CM | C64.1    | Malignant neoplasm of right kidney, except renal pelvis | Neoplasms          |
| ICD-10-CM | C20      | Malignant neoplasm of rectum                 | Neoplasms          |
| ICD-10-CM | C19      | Malignant neoplasm of rectosigmoid junction   | Neoplasms          |
| ICD-10-CM | C61      | Malignant neoplasm of prostate               | Neoplasms          |
| ICD-10-CM | C50.819  | Malignant neoplasm of overlapping sites of unspecified female breast | Neoplasms          |
| ICD-10-CM | C50.012  | Malignant neoplasm of nipple and areola, left female breast | Neoplasms          |
| ICD-10-CM | C06.9    | Malignant neoplasm of mouth, unspecified      | Neoplasms          |
| ICD-10-CM | C34.31   | Malignant neoplasm of lower lobe, right bronchus or lung | Neoplasms          |
| ICD-10-CM | C64.2    | Malignant neoplasm of left kidney, except renal pelvis | Neoplasms          |
| ICD-10-CM | C54.1    | Malignant neoplasm of endometrium            | Neoplasms          |
| ICD-10-CM | C62.11   | Malignant neoplasm of descended right testis  | Neoplasms          |
| ICD-10-CM | C50.111  | Malignant neoplasm of central portion of right female breast | Neoplasms          |
| ICD-10-CM | C67.9    | Malignant neoplasm of bladder, unspecified    | Neoplasms          |
| ICD-10-CM | C21.0    | Malignant neoplasm of anus, unspecified       | Neoplasms          |
| ICD-10-CM | C43.9    | Malignant melanoma of skin, unspecified       | Neoplasms          |
| ICD-10-CM | C80.1    | Malignant (primary) neoplasm, unspecified     | Neoplasms          |
| ICD-10-CM | C62.91   | Malig neopl of right testis, unsp descended or undescended | Neoplasms          |
| ICD-10-CM | C62.90   | Malig neoplasm of unsp testis, unsp descended or undescended | Neoplasms          |
| ICD-10-CM | D25.9    | Leiomyoma of uterus, unspecified              | Neoplasms          |
| ICD-10-CM | D25.1    | Intramural leiomyoma of uterus               | Neoplasms          |
| ICD-10-CM | D05.10   | Intraductal carcinoma in situ of unspecified breast | Neoplasms          |
### Table A1. Cont.

| ICD    | ICD-Code  | Diagnosis                                                                 | Categories     |
|--------|-----------|----------------------------------------------------------------------------|----------------|
| ICD-10-CM | C81.90   | Hodgkin lymphoma, unspecified, unspecified site                           | Neoplasms      |
| ICD-10-CM | D18.00   | Hemangioma unspecified site                                               | Neoplasms      |
| ICD-10-CM | D18.01   | Hemangioma of skin and subcutaneous tissue                                | Neoplasms      |
| ICD-10-CM | D47.3    | Essential (hemorrhagic) thrombocythemia                                   | Neoplasms      |
| ICD-10-CM | D09.9    | Carcinoma in situ, unspecified                                           | Neoplasms      |
| ICD-10-CM | D04.39   | Carcinoma in situ of skin of other parts of face                          | Neoplasms      |
| ICD-10-CM | D01.3    | Carcinoma in situ of anus and anal canal                                  | Neoplasms      |
| ICD-10-CM | D36.9    | Benign neoplasm, unspecified site                                         | Neoplasms      |
| ICD-10-CM | D27.9    | Benign neoplasm of unspecified ovary                                      | Neoplasms      |
| ICD-10-CM | D31.30   | Benign neoplasm of unspecified choroid                                     | Neoplasms      |
| ICD-10-CM | D12.3    | Benign neoplasm of transverse colon                                       | Neoplasms      |
| ICD-10-CM | D24.1    | Benign neoplasm of right breast                                           | Neoplasms      |
| ICD-10-CM | D36.10   | Benign neoplasm of peripheral nerves and autonomic nervous system,        | Neoplasms      |
| ICD-10-CM | D36.13   | Benign neoplasm of peripheral nerves and autonomic nervous system of      | Neoplasms      |
| ICD-10-CM | D11.0    | Benign neoplasm of parotid gland                                          | Neoplasms      |
| ICD-10-CM | D36.7    | Benign neoplasm of other specified sites                                  | Neoplasms      |
| ICD-10-CM | D10.39   | Benign neoplasm of other parts of mouth                                   | Neoplasms      |
| ICD-10-CM | D32.9    | Benign neoplasm of meninges, unspecified                                  | Neoplasms      |
| ICD-10-CM | D11.9    | Benign neoplasm of major salivary gland, unspecified                      | Neoplasms      |
| ICD-10-CM | D24.2    | Benign neoplasm of left breast                                            | Neoplasms      |
| ICD-10-CM | D13.7    | Benign neoplasm of endocrine pancreas                                     | Neoplasms      |
| ICD-10-CM | D33.3    | Benign neoplasm of cranial nerves                                         | Neoplasms      |
| ICD-10-CM | D21.9    | Benign neoplasm of connective and other soft tissue, unspecified          | Neoplasms      |
| ICD-10-CM | D21.10   | Benign neoplasm of connective and other soft tissue of unspecified        | Neoplasms      |
| ICD-10-CM | D12.6    | Benign neoplasm of colon, unspecified                                     | Neoplasms      |
| ICD-10-CM | D16.4    | Benign neoplasm of bones of skull and face                                | Neoplasms      |
| ICD-10-CM | D17.9    | Benign lipomatous neoplasm, unspecified                                   | Neoplasms      |
| ICD-10-CM | D17.20   | Benign lipomatous neoplasm of skin and subcutaneous tissue of unspecified| Neoplasms      |
| ICD-10-CM | D17.23   | Benign lipomatous neoplasm of skin and subcutaneous tissue of right leg  | Neoplasms      |
| ICD-10-CM | D17.21   | Benign lipomatous neoplasm of skin and subcutaneous tissue of right arm  | Neoplasms      |
| ICD-10-CM | D17.24   | Benign lipomatous neoplasm of skin and subcutaneous tissue of left leg   | Neoplasms      |
| ICD-10-CM | D17.22   | Benign lipomatous neoplasm of skin and subcutaneous tissue of left arm   | Neoplasms      |
| ICD-10-CM | D17.0    | Benign lipomatous neoplasm of skin and subcutaneous tissue of head,      | Neoplasms      |
| ICD-10-CM | C44.611  | Basal cell carcinoma skin/ unsp upper limb, inc shoulder                  | Neoplasms      |
| ICD-10-CM | C44.91   | Basal cell carcinoma of skin, unspecified                                 | Neoplasms      |
| ICD-10-CM | C44.41   | Basal cell carcinoma of skin of scalp and neck                            | Neoplasms      |
| ICD-10-CM | C44.319  | Basal cell carcinoma of skin of other parts of face                       | Neoplasms      |
| ICD-10-CM | C44.519  | Basal cell carcinoma of skin of other part of trunk                      | Neoplasms      |
| ICD-10-CM | C44.311  | Basal cell carcinoma of skin of nose                                      | Neoplasms      |
| ICD-10-CM | ICD-Code | Diagnosis | Categories |
|-----------|----------|-----------|------------|
| ICD-10-CM | Z34.81   | Encounter for supervision of normal pregnancy, first trimester | Pregnancy |
| ICD-10-CM | Z34.80   | Encounter for supervision of other normal pregnancy, unspecified trimester | Pregnancy |
| ICD-10-CM | Z34.83   | Encounter for supervision of other normal pregnancy, third trimester | Pregnancy |
| ICD-10-CM | Z34.82   | Encounter for supervision of other normal pregnancy, second trimester | Pregnancy |
| ICD-10-CM | Z34.90   | Encounter for supervision of normal pregnancy, unspecified, unspecified trimester | Pregnancy |
| ICD-10-CM | Z34.91   | Encounter for supervision of normal pregnancy, unspecified, first trimester | Pregnancy |
| ICD-10-CM | Z34.00   | Encounter for supervision of normal first pregnancy, unspecified trimester | Pregnancy |
| ICD-10-CM | Z34.01   | Encounter for supervision of normal first pregnancy, third trimester | Pregnancy |
| ICD-10-CM | Z34.02   | Encounter for supervision of normal first pregnancy, second trimester | Pregnancy |
| ICD-10-CM | Z32.00   | Encounter for pregnancy test, result unknown | Pregnancy |
| ICD-10-CM | Z32.01   | Encounter for pregnancy test, result positive | Pregnancy |

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