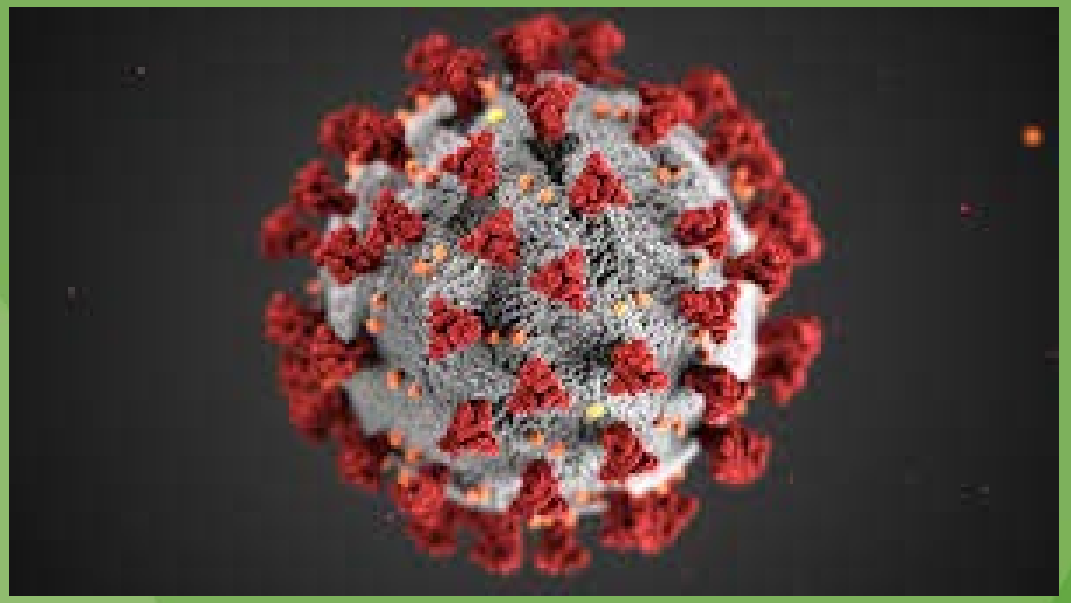
# Hot Topics: COVID-19




**Marcie Riches, MD, MS**

University of North Carolina

Scientific Director, CIBMTR Infection and Immune Reconstitution Working Committee

**Jenni Bloomquist**, Manager Clinical Data Quality, CIBMTR

**Kavita Bhavsar**, CRC, CIBMTR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The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW).

# Conflict of Interest Disclosure

Consulting or Advisory Role: BioIntellect

Research Funding: Jazz (Inst), Atara Biotherapeutics (Inst).

No conflicts as pertains to this presentation

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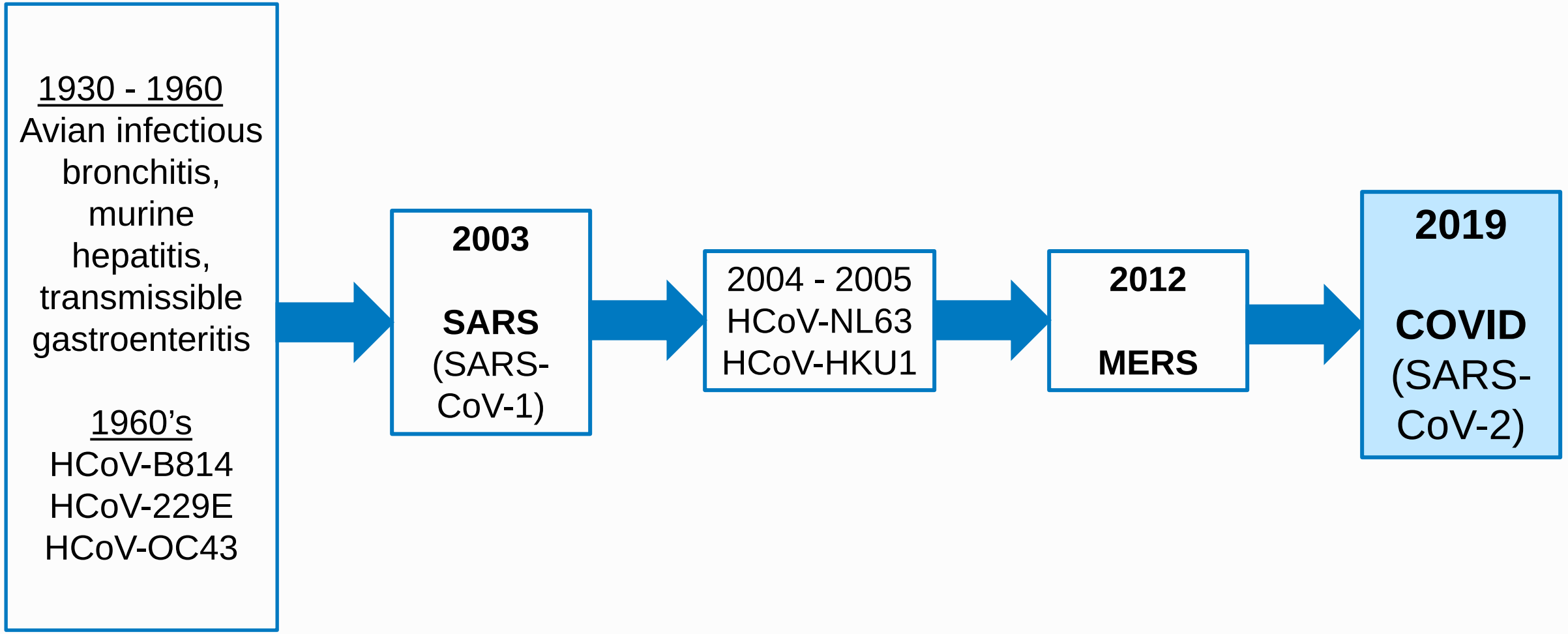
# Overview

- Background on Coronaviruses
- Review transplant community response
- Discuss 2149 form and CIBMTR COVID website
- Review published data on HCT/CT patients
- Present data on CIBMTR patients with COVID-19

# Coronaviruses – yes, multiple

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# SARS-CoV-2

- 82% identical to the SARS-CoV-1 (SARS) from 2003[1]
- Household transmission rate ~15%[2]
- $R_0$ 1: 1.4-3[3]


As of **01/09/2021**[4]:

Worldwide: 89,516,439 cases and 1,924,004 deaths

US: 22,095,975 cases and 371,989 deaths

[1]Wu et al, Nature 2020; 579: 265-269

[2]Bi et al, Lancet Infect Dis 2020; 20:911-919

[3]Sanche et al, Emerg Infect Dis J 2020; 26:1-19

[4]https://coronavirus.jhu.edu/map.html

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# HCT/CT Community Response

- Guidelines published from ASTCT, EBMT, CAR T-cell Consortium
- NMDP, WMDA, and DKMS provided guidance regarding unrelated donors
  - New donor questionnaire from NMDP
- CIBMTR rapidly analyzed data regarding
  - outcomes with cryopreservation for patients receiving PTCy and SAA
  - Impact of Tocilizumab on infection risks

# Guidelines: Patients

- Defer non-urgent HCT (non-malignant disease)
- Test patients within 48 – 72 hours of lymphodepleting chemotherapy/conditioning
- Exposure prior to HCT
  - Delay 14 – 21 days if low risk indication for HCT
- COVID-19 infection identified prior to HCT
  - AutoHCT: Delay 3 months
  - AlloHCT: Delay until symptom resolution and 2 negative PCR tests weekly/at least 24h apart

Ardura et al, BBMT May 2020
Ljungman et al, BMT May 2020
Waghmare et al, BBMT July 2020

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# Guidelines:  Patients

- Use cryopreserved cells if able
  - Exceptions – SAA
- Peripheral blood stem cells preferred over marrow
  - Exceptions – Pediatrics, SAA
- Decrease transfusion thresholds
- If high suspicion of COVID infection but nasal swab negative, consider early bronchoscopy

Ardura et al, BBMT May 2020
Ljungman et al, BMT May 2020
Waghmare et al, BBMT July 2020
Bachanova et al, BBMT July 2020
Chhabra et al, BBMT June 2020

# Guidelines: Donors

| | |
|---|---|
| **Confirmatory Typing** | Consider donor work-up and confirmatory typing simultaneously |
| **History of COVID-19 infection** | - Defer collection for at least 28 days after recovery<br><br>*If HCT need is urgent, donor is completely well and there are no alternative donors, earlier collection may be considered* |
| **Donors who have contact with a confirmed COVID-19 case** | - Defer collection for 4 weeks after the exposure<br><br>*If HCT need is urgent, donor is completely well and there are no alternative donors, earlier collection may be considered* |
| **Donors who have traveled internationally or reside in a high risk country** | https://share.wmda.info/pages/viewpage.action?pageId=344866320#/ |

WMDA and Be The Match guidelines
Algwaiz et al, BBMT Dec 2020
Mengling et al, BMT Nov 2020

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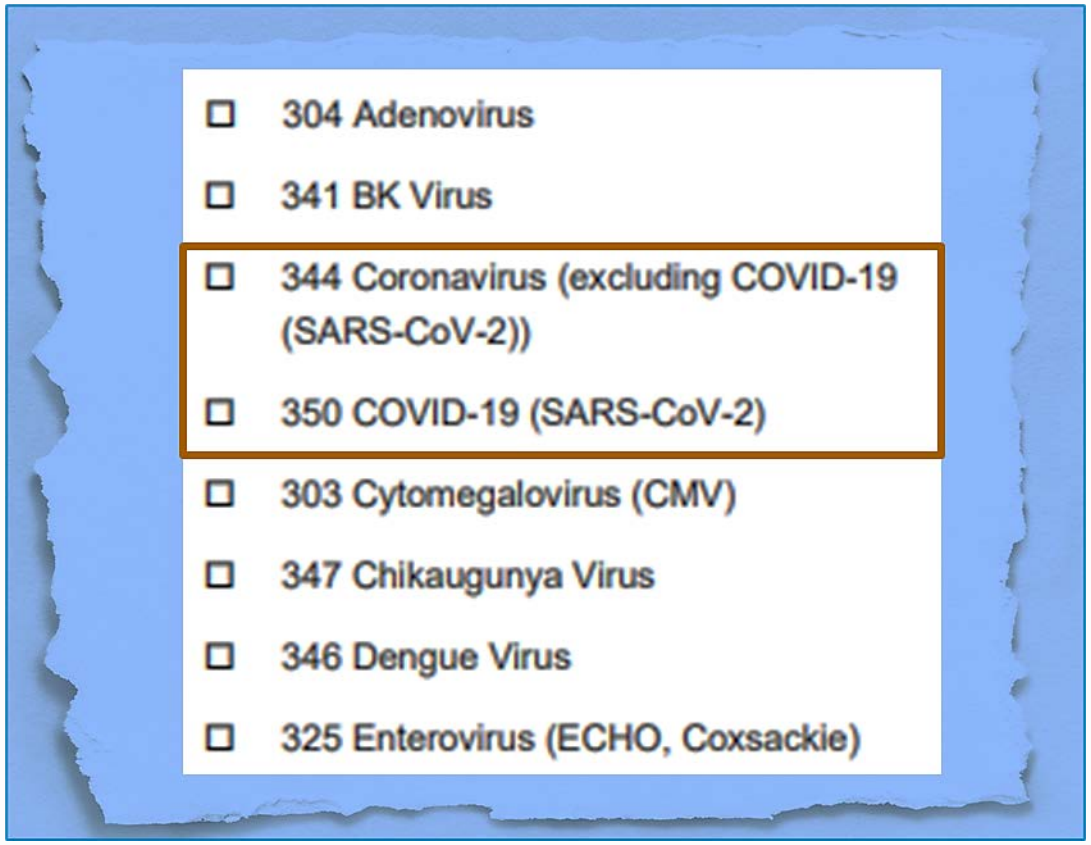
# COVID-19 Infection in HCT/CT patients

- Requires coordinated data collection
- Prior to 3/26/2020
  - 2100 and 4100 collected data on “Coronavirus” [org 344]
- 3/27/2020
  - Added COVID-19 (SARS-CoV-2) [org 350]
  - 2149 form implemented to obtain info about COVID-19 in HCT/CT patients

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# Form 2149: Respiratory Virus Form

- Previously designed and vetted by DM group but not implemented
- Allowed rapid (~2 weeks) modification so CIBMTR could collect data on infected HCT/CT patients
  - Added date of infection
  - Added “Other, specify” fields
- Goal: Collect information on diagnosis, risk factors, and treatment/response to therapy

# Form 2149: Diagnosis

- Collect information on tests with a positive result supporting the diagnosis
  - New testing methods became available allowing an “other, specify” field

- Tests performed 7 days before and up to 14 days after the reported date of infection
  - Provides have global picture of certainty of diagnosis

# Form 2149: Diagnosis

1. Date of infection diagnosis: __ __ __ __ / __ __ / __ __
   YYYY MM DD

**For questions 2 - 6, report all positive testing used to determine the diagnosis of the respiratory viral infection. Testing should be obtained between 7 days prior to 14 days after the diagnosis.**

2. Specify positive diagnostic tests used to determine the diagnosis of the respiratory viral infection **(check all that apply)**
   - ☐ Nasal swab/wash
   - ☐ Lung fluid from bronchoalveolar lavage (BAL)
   - ☐ Histopathology findings of viral cytopathic changes **(biopsy)**
   - ☐ Culture
   - ☐ Other → 3. Specify:_____

4. Were there any positive radiographic findings supporting the infection diagnosis? **(e.g., x-ray, CT, or MRI)**
   - ☐ Yes →
     5. Specify imaging sites **(check all that apply)**
        - ☐ Chest
        - ☐ Sinus
        - ☐ Other imaging site → 6. Specify other imaging site:_____
   - ☐ No
   - ☐ Unknown

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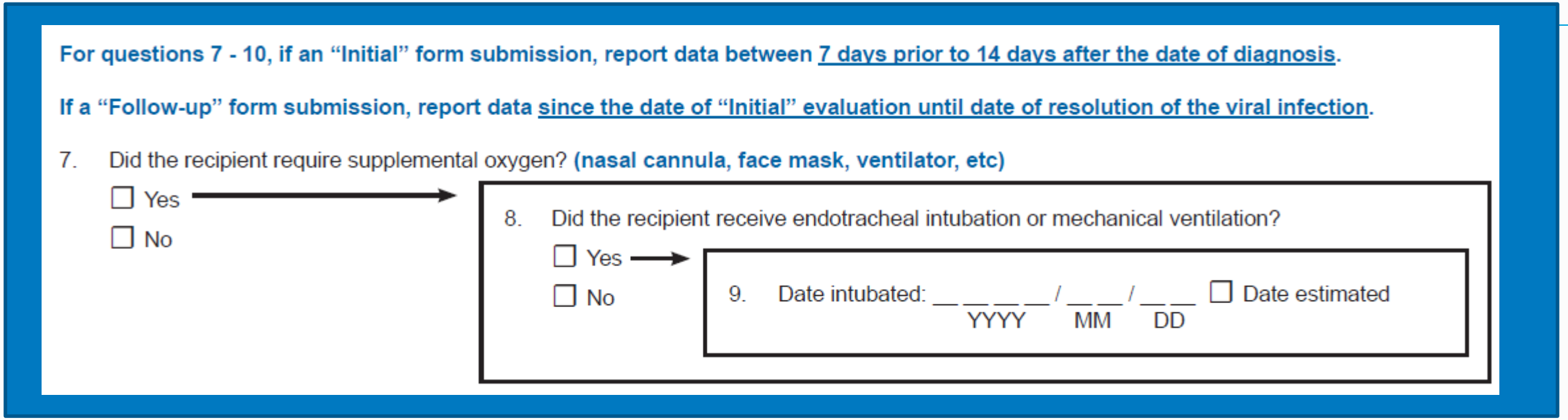
# Form 2149: Clinical Factors



For questions 7 - 10, if an "Initial" form submission, report data between 7 days prior to 14 days after the date of diagnosis.

If a "Follow-up" form submission, report data since the date of "Initial" evaluation until date of resolution of the viral infection.

7. Did the recipient require supplemental oxygen? (nasal cannula, face mask, ventilator, etc)
   - ☐ Yes →
   - ☐ No

8. Did the recipient receive endotracheal intubation or mechanical ventilation?
   - ☐ Yes →
   - ☐ No

9. Date intubated: __ __ __ __ / __ __ / __ __ (YYYY / MM / DD) ☐ Date estimated

- Oxygen needs
  - Supplemental Oxygen
  - Ventilator support
- Steroid use
- Lab parameters
  - WBC count and differential
- Immune system parameters
  - IgG levels

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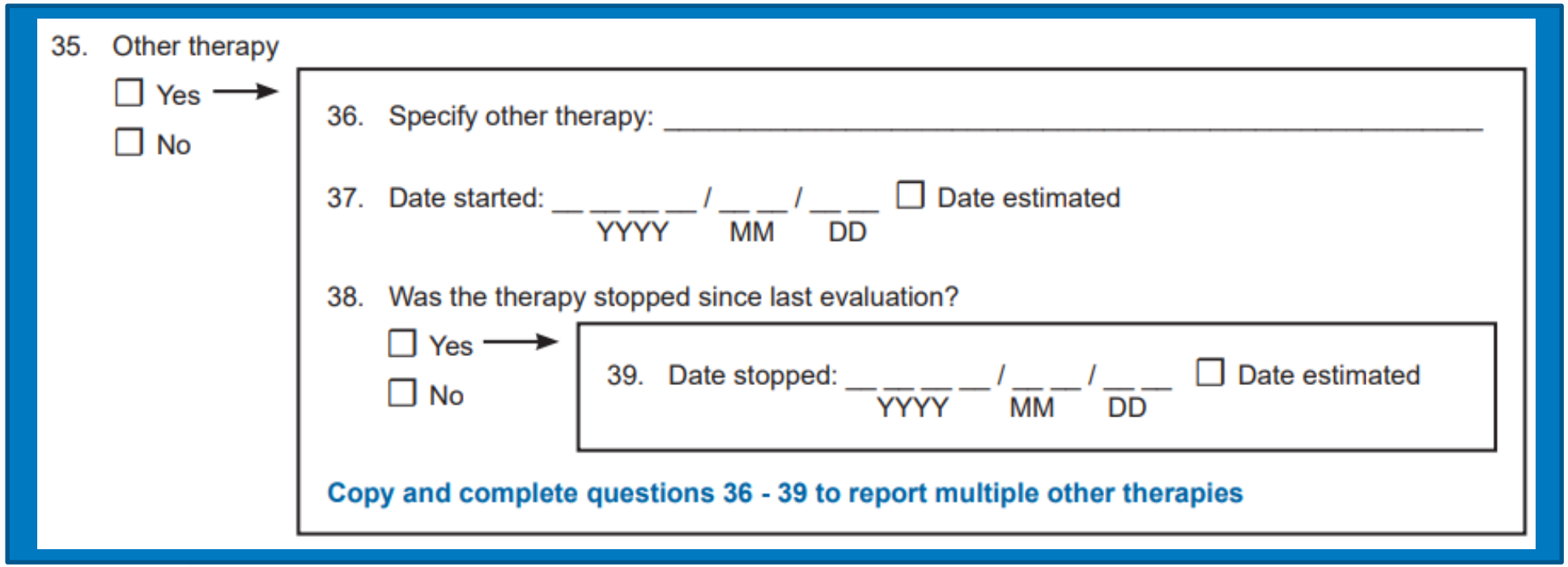
# Form 2149: Therapy

- Unknown what treatments worked but many things being tested
  - Elected not to change the previously designed treatment options
- Added Other Therapy, Specify


35. Other therapy

☐ Yes →

☐ No

36. Specify other therapy: _____

37. Date started: __ __ __ __ / __ __ / __ __ ☐ Date estimated
YYYY MM DD

38. Was the therapy stopped since last evaluation?

☐ Yes →

☐ No

39. Date stopped: __ __ __ __ / __ __ / __ __ ☐ Date estimated
YYYY MM DD

**Copy and complete questions 36 - 39 to report multiple other therapies**

# Therapy

| Benefit Seen | No benefit | May Work | |
|---|---|---|---|
| Remdesivir | Azithromycin* | Lopinovir/ritonavir | Mesenchymal stromal cells* |
| Tocilizumab* | Chlorquine | Favipiravir | Ibrutinib* |
| Convalescent plasma | Hydroxychloroquine* | Eculizumab* | Steroids* |
| | | Siltuximab* | Ruxolitinib* |

* Have role in HCT/CT management outside of COVID-19

Patients often on other antimicrobials to minimize risk of super-infections

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Algwaiz et al, BBMT 2020; 26(12): 2181-2189

# Form 2149: Infection Status and Follow-up

40. What was the status of the infection? **(If the status is captured as "Ongoing" or "Improved", an additional Respiratory Virus Post-Infusion Form (2149) will come due. The "Follow-up" form should be completed once the viral infection has resolved).**

- ☐ Death - ***Go to question 41***
- ☐ Ongoing - ***Go to question 41***
- ☐ Improved - ***Go to question 41***
- ☐ Resolved - ***Go to question 41***
- ☐ Unknown - ***Go to signature line***

41. Date of evaluation: __ __ __ __ / __ __ / __ __ ☐ Date estimated
YYYY MM DD

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# Form 2149: Infection Status and Follow-up

| Status | Definition | Follow-up form due |
|---|---|---|
| Death | Died without resolution of infection | No |
| Ongoing | Infection continues without significant improvement at time of evaluation | Yes |
| Improved | On-going treatment for infection although signs/symptoms resolved | Yes |
| Resolved | Signs/symptoms now absent and therapy course completed | No |
| Unknown | No information on status of infection | N/A |

Follow-up Form: Collects data from the time of the initial report evaluation until resolution of the infection or by death

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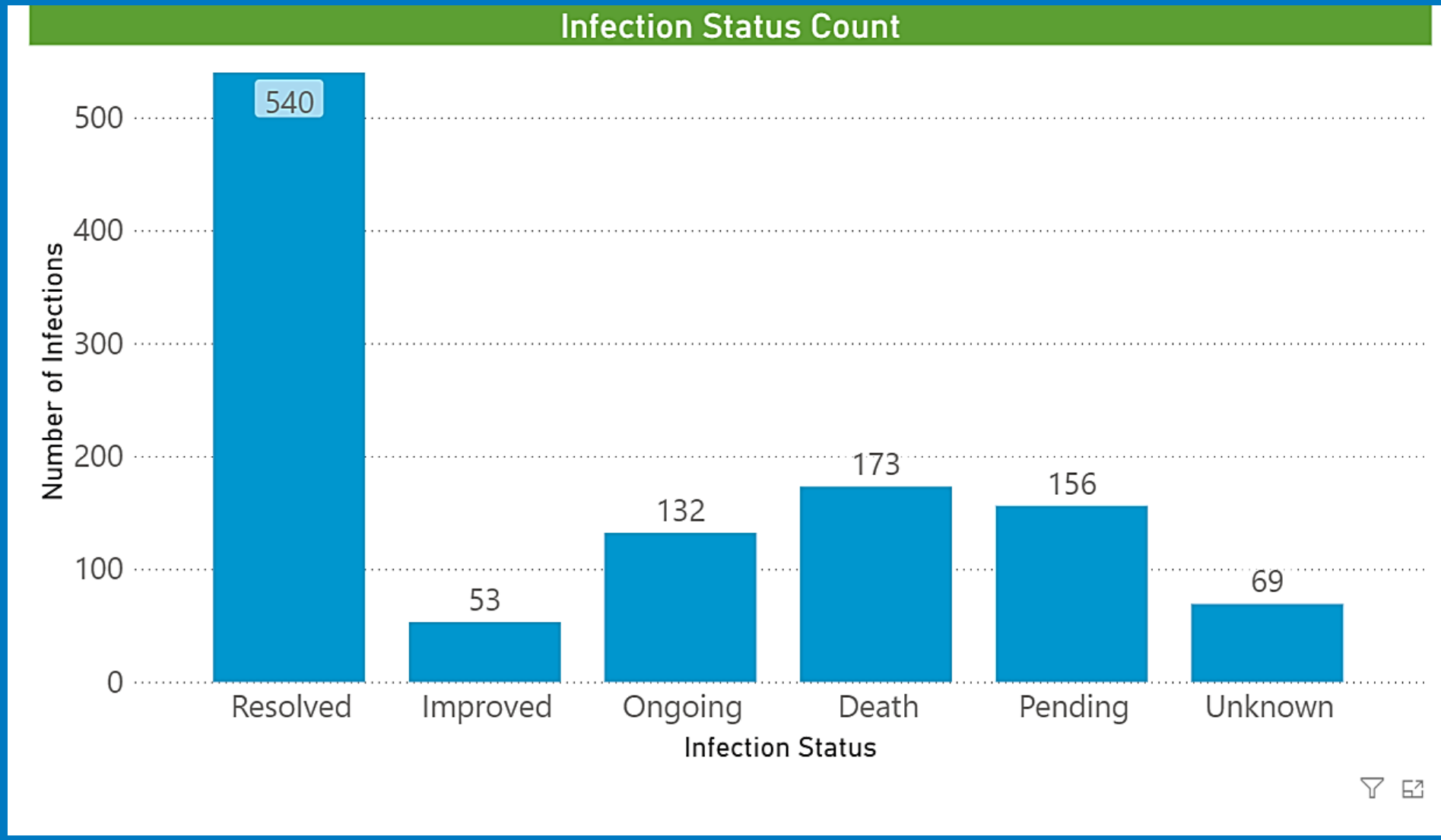
# Data Quality Tips

- Better to estimate dates than to leave date blank
  - Refer to Forms Instruction Manual for guidance on estimating dates
- Don’t leave questions blank when an “UNKNOWN” response is provided
- Double check spelling/extra punctuation when using the specify fields
- Make sure you are answering all relevant questions – like Unit of Measure when supplying a lab value
- Upload supporting documentation when the data are difficult to fit into the form

# COVID-19 Reported Data

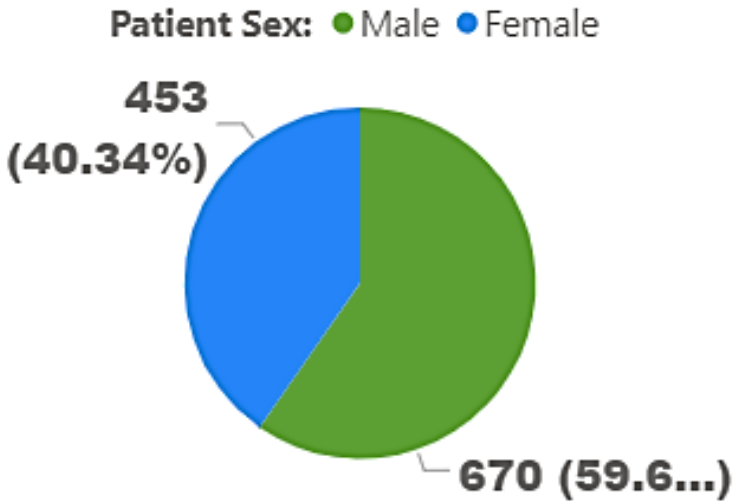
- https://www.cibmtr.org/Covid19/Pages/default.aspx
- Data updated real time
- Site allows individuals to review data breakdown by several variables
  - Patient Sex
  - Type of Cellular Therapy
  - Age at infection
  - US Region
  - Time from infusion

# # of COVID 19 infections: 1,127
# # of Centers Reporting: 187 (154 US, 33 non-US)

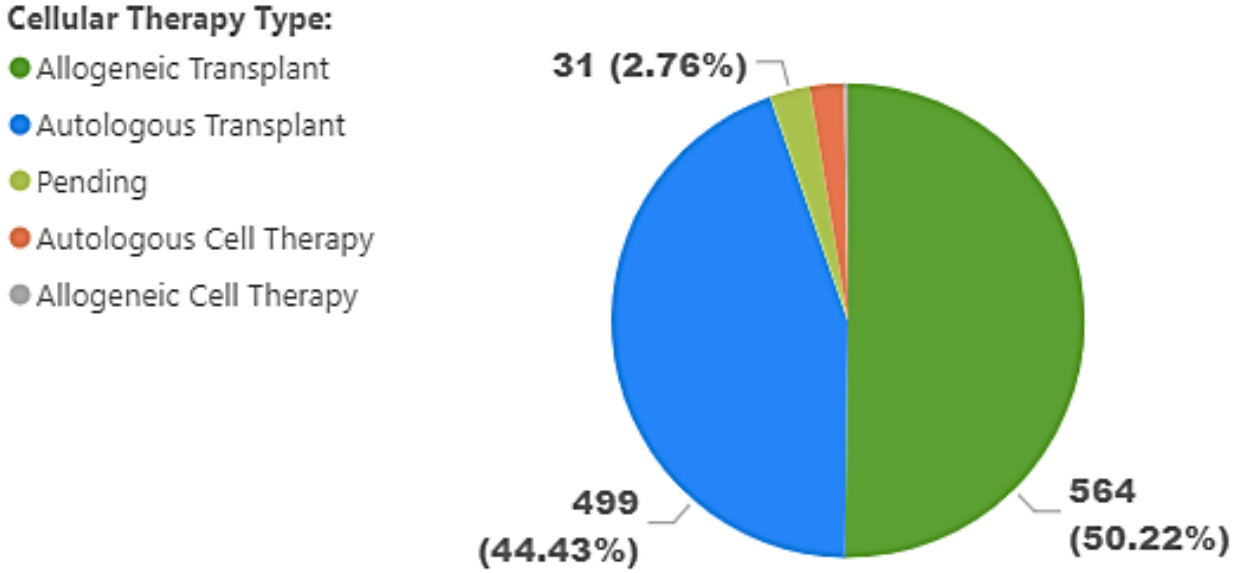



Data as of 01/01/2021

## Patient Sex




## Cellular Therapy Type



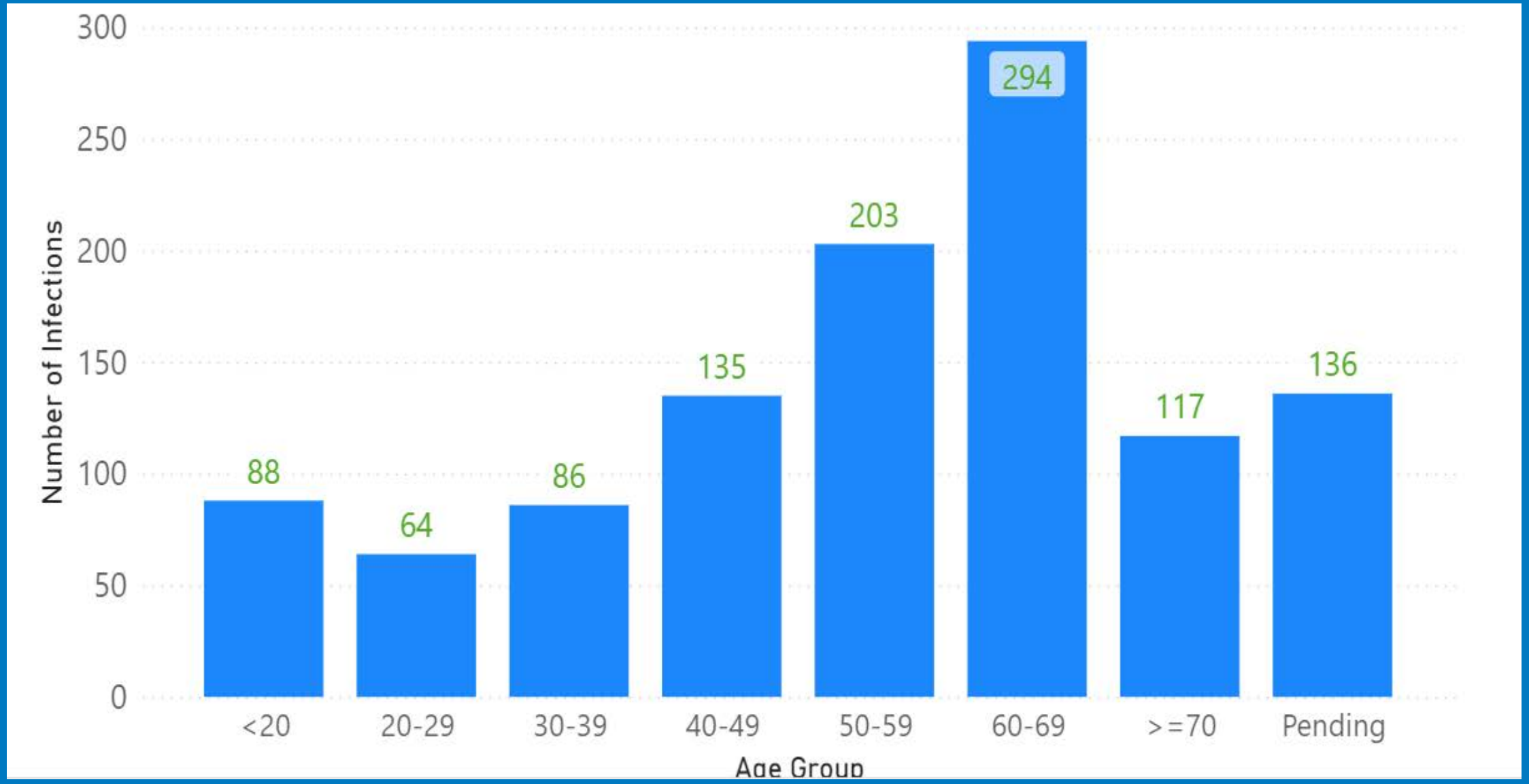

~ 60% Male

HCT Patients account for 95% of the patients

Other cell therapy (i.e. CAR-T) ~2.5% of patients

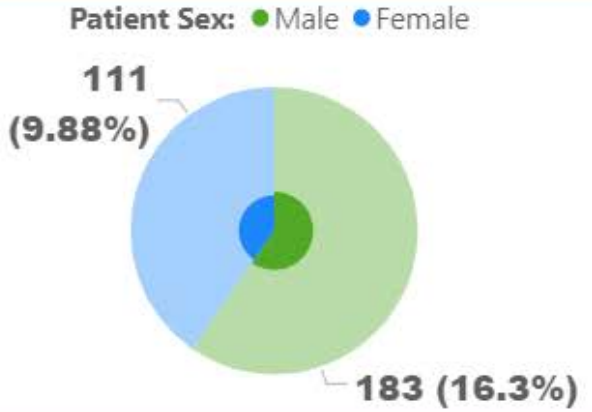
Data as of 01/01/2021

# Age at COVID-19 Diagnosis

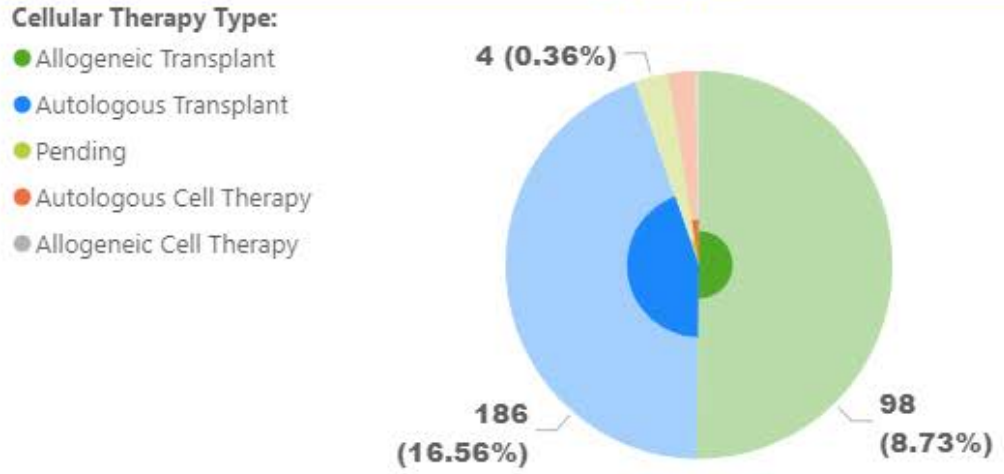



Data as of 01/01/2021

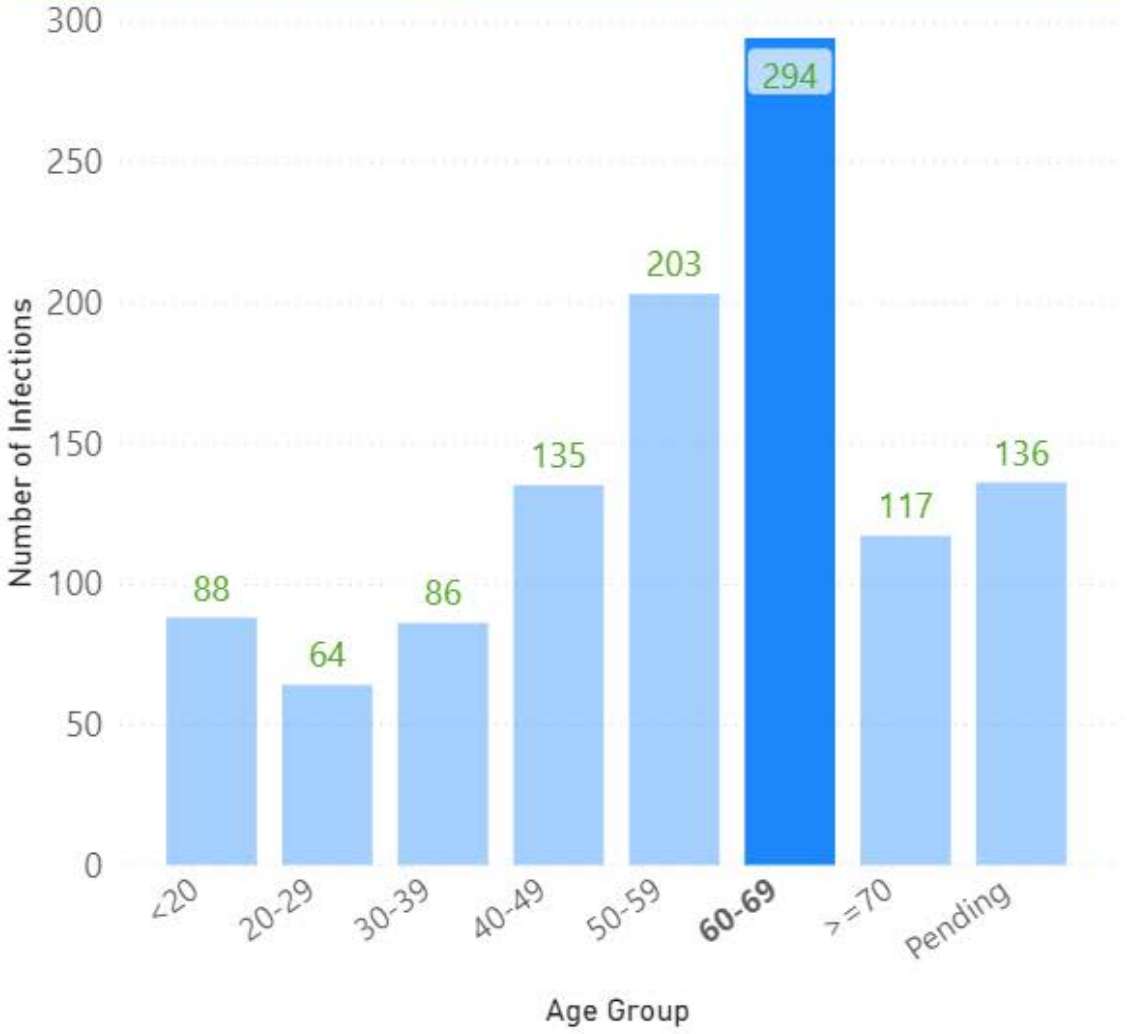
## Patient Sex




## Cellular Therapy Type




## Age at Infection

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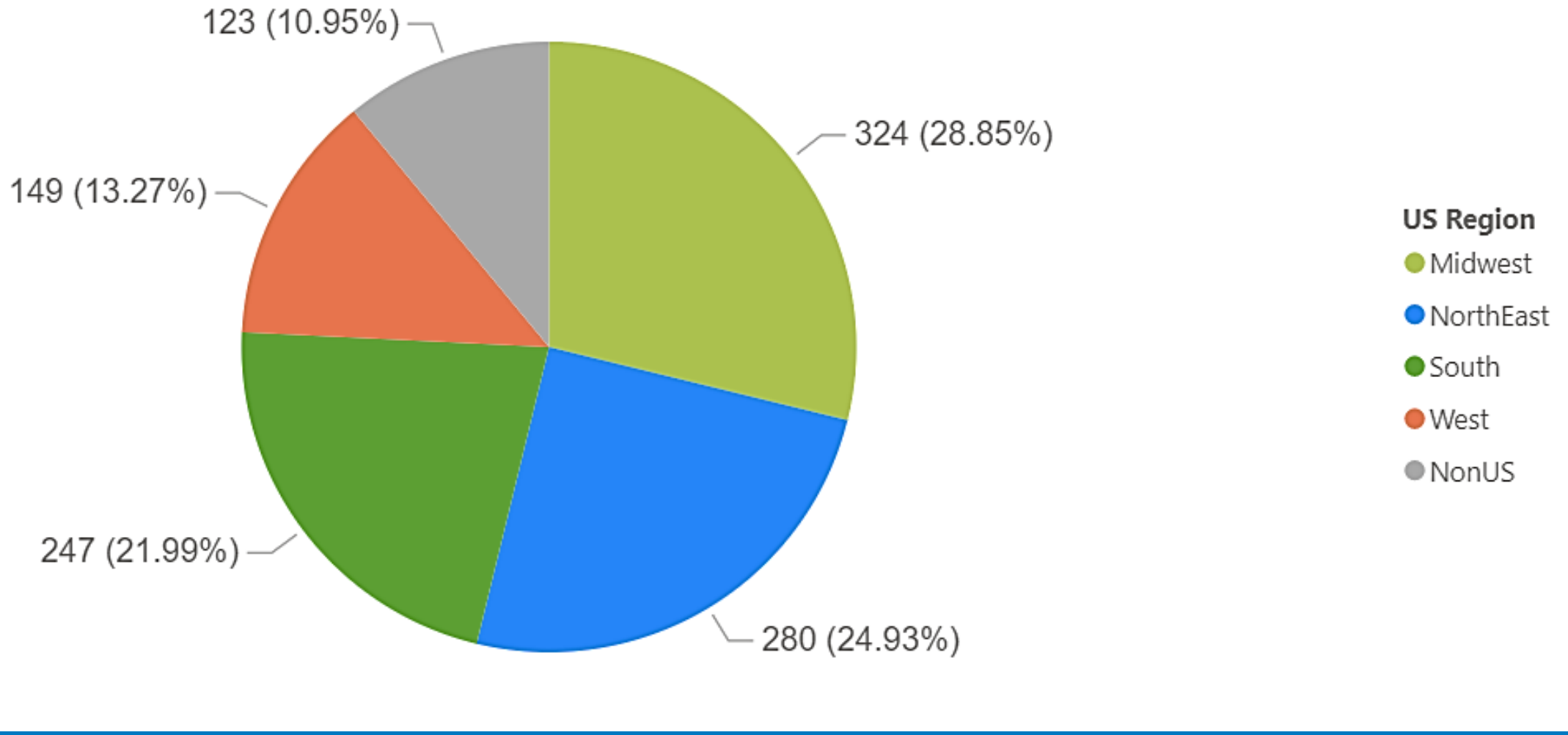
Data as of 01/01/2020

# Infections by Region

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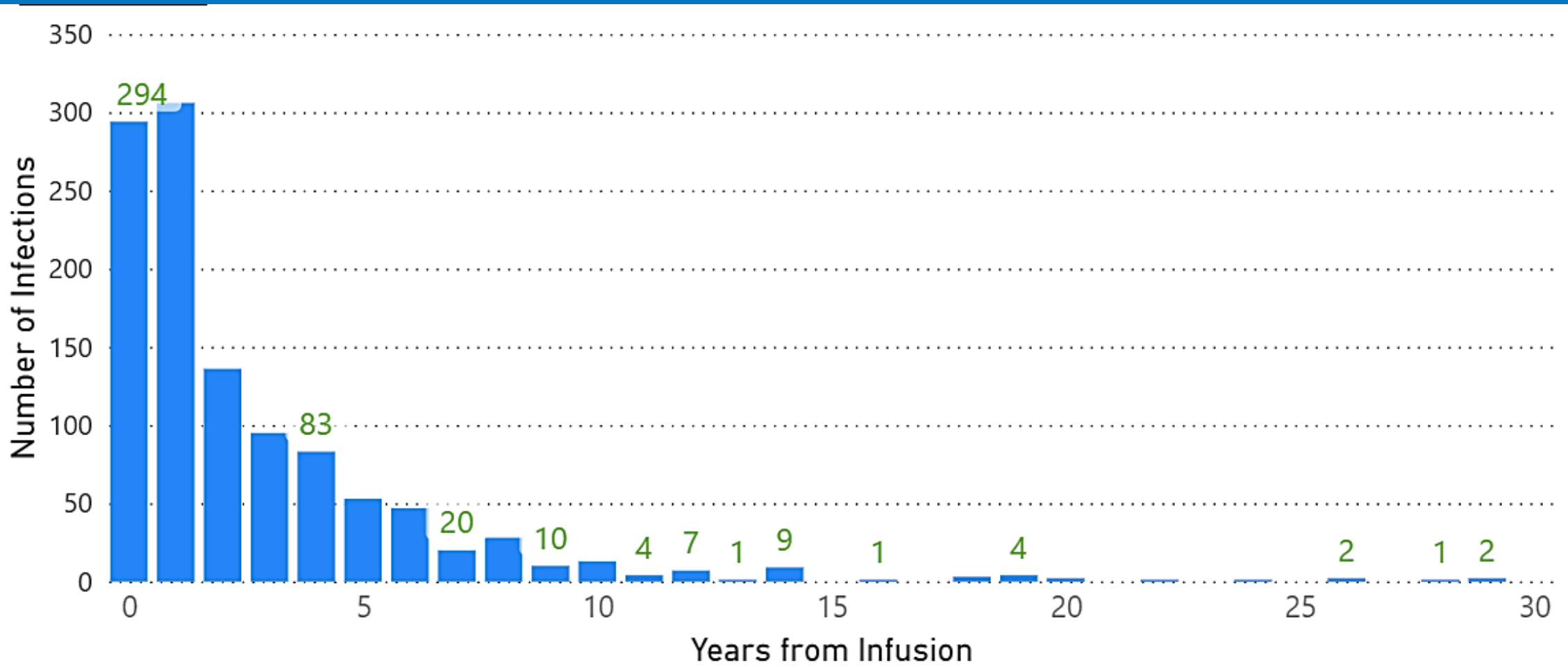
Data as of 01/01/2021

# Time from cell infusion to COVID-19 Infection




Data as of 01/01/2021

# Published reports (non-CIBMTR)

| Author/Citation | Population/Details | Outcomes |
|---|---|---|
| Kanellopoulos<br>BJH, June 2020 | Birmingham Heartlands Hospital<br>1 Auto/6 Allo (MUD=3, Haplo=2, mMUD=1)<br>Time from HCT to COVID: 61 days (7 – 343) | 3 deaths (2 COVID, 1 relapse) at median of 22 days from COVID |
| Pinana<br>Exp Hem Onc, Aug 2020 | 41 hospitals in Spain<br>58 Auto/65 Allo (Sib=29, unrelated = 22, Haplo = 14)<br>Time from HCT to COVID: Auto ~26 months; Allo ~14.5 months | Overall mortality at day 45: Auto 17%, Allo 18%<br>*Increased risk of death with age >70, active cancer, neutropenia, increased CRP* |
| Varma<br>BMT, Aug 2020 | 4 US Centers (Rush, U Chicago, NMH, Mount Sinai)<br>14 Auto/20 Allo<br>Time from HCT to COVID: Auto ~13 months; Allo ~19 months | 7 deaths (5 allo, 2 auto) at a median 15 days from COVID |
| Altuntas<br>BMT, Oct 2020 | Turkey<br>32 HCT (20 Auto/12 Allo) + 465 Heme Malignancy + 497 patients without cancer | HCT: 15.6% died<br>HM: 11.8% died<br>No Cancer: 5.6% died |

# Published reports (non-CIBMTR)

| Author/Citation | Population/Details | Outcomes |
|---|---|---|
| Coll<br>Am J Transplant,<br>Oct 2020 | Spain SOT/HCT patients<br>41 Auto/71 Allo<br>Time from HCT to COVID: Auto 18 months (4 – 53);<br>Allo 15 months (7 – 37) | Auto: 24% died<br>Allo: 20% died<br>Overall survival @30 days<br>~80% |
| Sultan<br>BMT, Oct 2020 | Nasser's Institute<br>7 Allo MRD<br>Time from HCT to COVID: 8 months (3 – 113) | All survived at a f/u of 84 days |
| Shah<br>JCI Nov 202 | MSKCC<br>37 Auto/35 Allo/5 CAR-T<br>Time from cell therapy to COVID: 25.7 months | Overall survival @ 30 days<br>Allo = 73%, Auto = 87%,<br>CAR-T = 60%<br>*Increased risk of death with co-morbidities, infiltrates, and neutropenia* |

# Prolonged shedding of viable virus

- Initial report from MSKCC
  - 45 patients had a second nasopharyngeal swab
    - 52% negative by 28 days (22 – 35 days)
    - 48% still positive at a median of 44 days (23 – 57)
- Follow-up analysis of 20 patients
  - Median duration of shedding 51 days from onset of symptoms
  - Viable virus identified in 5 patients @ 8, 17, 25, 26, and 61 days

Shah et al, J Clin Investigation 2020; 130(12)
Aydillo et al, NEJM 2020; 383(26)

# CIBMTR INWC CV20-04

- Reviewed initial cohort of patients reported on the 2149 between 03/27/20 – 08/12/2020
  - 318 patients (184 Allo, 134 Auto)
- Aims:
  1. Describe the characteristics of TCT patients with a COVID-19 infection
  2. Describe the severity of COVID-19 infection in TCT patients
  3. Describe the treatment approaches for COVID-19 in TCT patients
  4. Describe the survival of TCT patients after infection with COVID-19

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# Early Analysis: 03/27/20 – 08/12/2020

| Variable | Allogeneic N = 184 | Autologous N = 134 |
|---|---|---|
| Age, y, median (range) | 47y (<1 – 76) | 60y (2 – 78) |
| Male (%) | 107 (58%) | 81 (60%) |
| Race (%) | | |
| Caucasian | 141 (77%) | 74 (55%) |
| African American | 13 ( 7%) | 33 (25%) |
| Other/Missing | 9 (5%)/21 (11%) | 8 (6%)/19 (14%) |
| Region (%) | | |
| US | 153 (83%) | 123 (92%) |
| Non-US | 31 (17%) | 11 ( 8%) |

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Sharma et al, *Lancet Hematology, 2021*

# Early Analysis: 03/27/20 – 08/12/2020

| Variable | Allogeneic<br>N = 184 | Autologous<br>N = 134 |
|---|---|---|
| Disease (%) | | |
| AML/ALL/MDS/MPN | 143 (78%) | 2 ( 1%) |
| Lymphoma | 18 (10%) | 41 (31%) |
| Myeloma | 4 ( 2%) | 86 (64%) |
| Other malignant | 8 ( 5%) | 4 ( 3%) |
| Other non-malignant | 11 ( 6%) | 1 (<1%) |
| Time from HCT to COVID-19, months, Median (IQR) | N = 165<br>**17 months (8 – 46)** | N = 116<br>**23 months (8 – 51)** |

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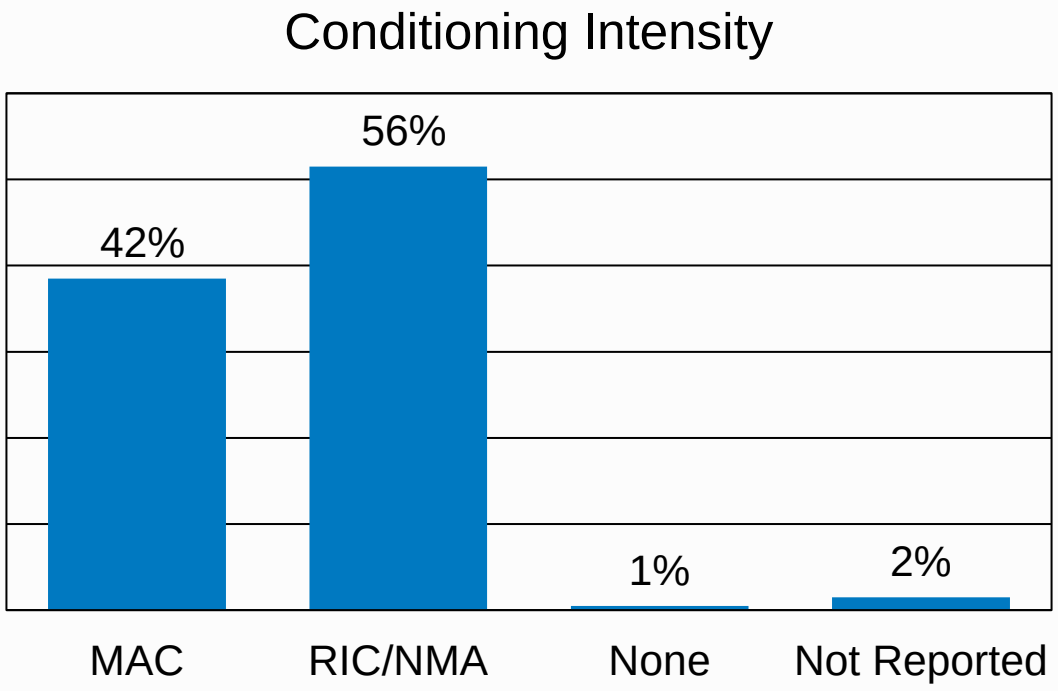
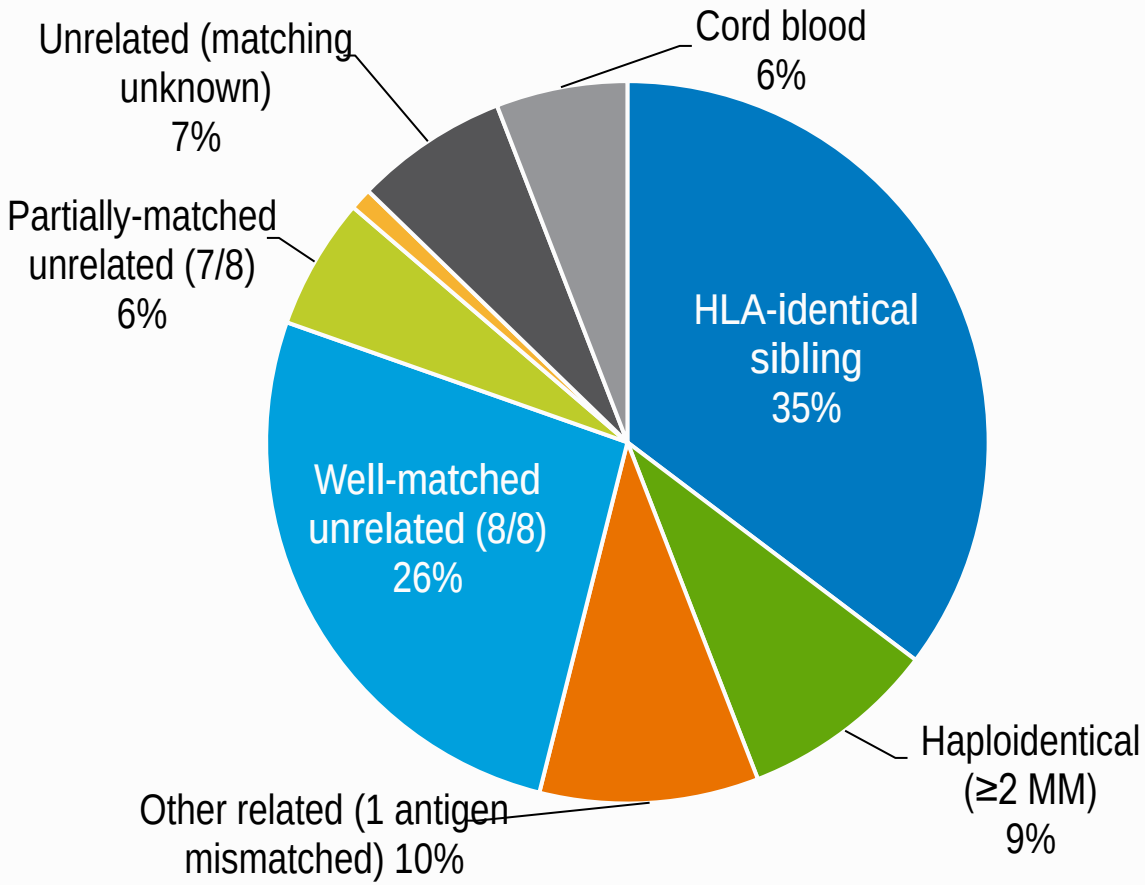
Sharma et al, *Lancet Hematology, 2021*

# Allogeneic HCT Characteristics




Received TBI: 45%
Received ATG/Alemtuzumab: 18%




PBSC: 76%, BM: 18% & UCB: 6%

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Sharma et al, *Lancet Hematology, 2021*

# Baseline Characteristics - COVID-19

| | AlloHCT (N = 184) | AutoHCT (N = 134) |
|---|---|---|
| Follow-up from COVID-19 diagnosis in days - median (range) | 21 (1 - 93) | 25 (1 - 109) |
| | | |
| Severity of infection - no. (%) | | |
| Mild: No supplemental $O_2$ or mechanical ventilation | 86 (47%) | 69 (51%) |
| Moderate: Supplemental $O_2$ only | 49 (27%) | 27 (20%) |
| Severe: Mechanical ventilation and supplemental $O_2$ | 28 (15%) | 17 (13%) |
| Not reported | 21 (11%) | 21 (16%) |

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Sharma et al, *Lancet Hematology, 2021*

| Treatment* | Mild disease (no Oxygen) | | Moderate/Severe Disease (Oxygen ± Mechanical Ventilation require) | | Disease Severity unknown | |
|---|---|---|---|---|---|---|
| | AlloHCT (n=86) | AutoHCT (n=69) | AlloHCT (n=77) | AutoHCT (n = 44) | AlloHCT (n=21) | AutoHCT (n = 21) |
| No meds reported | 2 | 0 | 2 | 0 | 20 | 20 |
| No treatment given | 57 | 44 | 13 | 8 | 0 | 1 |
| Convalescent plasma | 2 | 1 | 9 | 6 | 1 | 0 |
| Remdesivir | 2 | 4 | 22 | 9 | 1 | 0 |
| Tocilizumab | 0 | 0 | 4 | 3 | 0 | 0 |
| Hydroxychloroquine | 4 | 7 | 18 | 11 | 0 | 0 |
| Azithromycin | 7 | 3 | 5 | 1 | 0 | 0 |
| Lopinovir/Ritonovir | 0 | 1 | 0 | 0 | 0 | 0 |
| Methylprednisolone | 0 | 0 | 1 | 1 | 0 | 0 |
| Oseltamivir | 1 | 0 | 3 | 2 | 0 | 0 |
| Ribavirin | 0 | 1 | 0 | 0 | 0 | 0 |
| DAS181 | 0 | 0 | 1 | 0 | 0 | 0 |
| Acyclovir/Valacyclovir | 7 | 5 | 7 | 4 | 0 | 0 |
| Famciclovir | 0 | 0 | 0 | 1 | 0 | 0 |
| Antibacterial agent | 2 | 7 | 6 | 9 | 0 | 0 |
| Other drug† | 3 | 1 | 1 | 0 | 0 | 0 |

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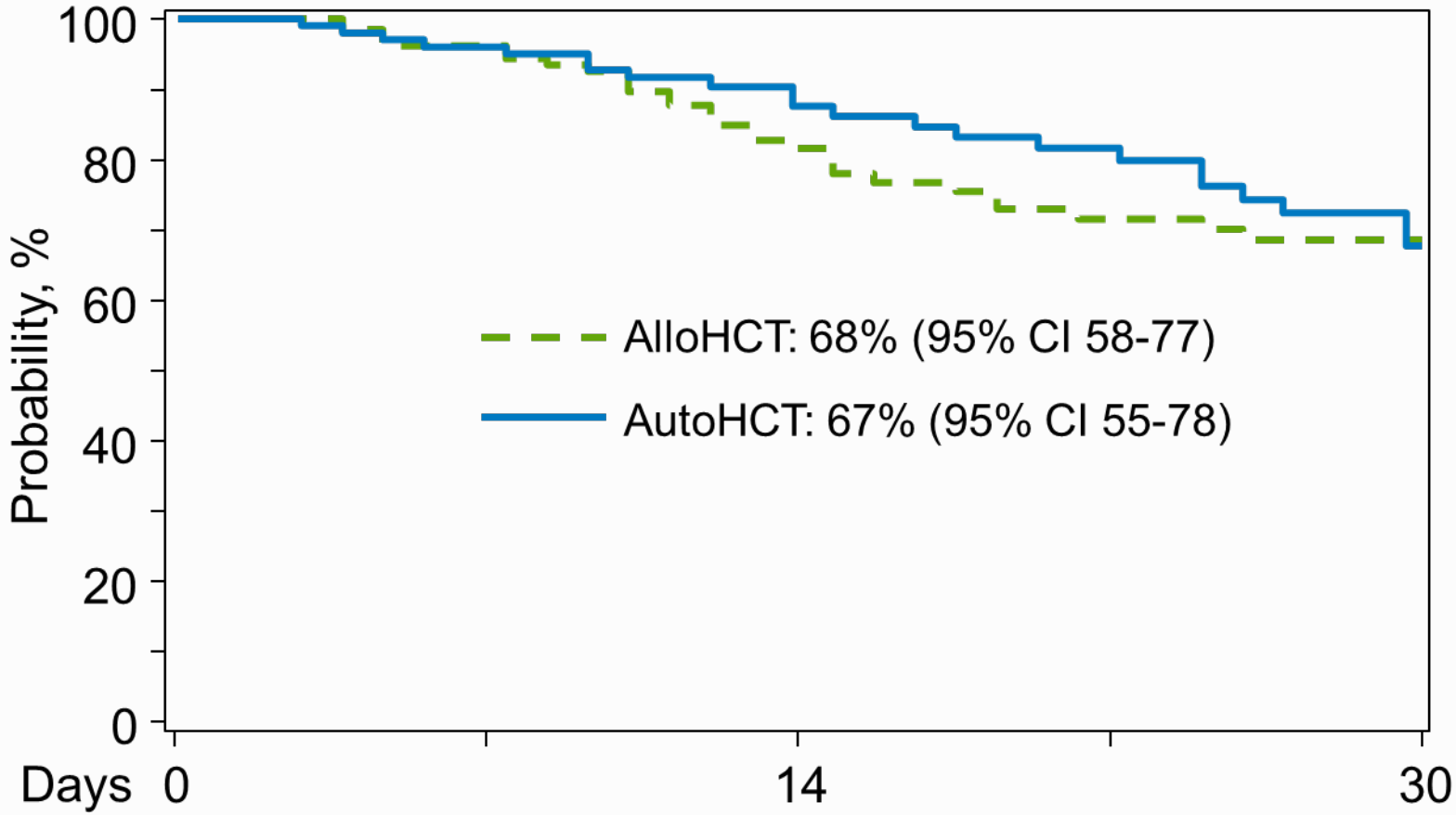
Sharma et al, *Lancet Hematology, 2021*

# Overall survival following COVID-19 diagnosis




| # at Risk (# censored) | | | |
|---|---|---|---|
| AlloHCT | 153 (0) | 71 (62) | 39 (83) |
| AutoHCT | 109 (0) | 65 (34) | 28 (58) |

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Sharma et al, *Lancet Hematology, 2021*

# Factors associated with increased risk of death

## Allogeneic HCT

| | # Events/ # Evaluable | HR (95% CI) | P-value |
|---|---|---|---|
| Age | | | 0.020 |
| < 50y | 10/85 | 1.00 | |
| ≥ 50y | 26/68 | **2.53 (1.16-5.52)** | |
| Sex | | | 0.006 |
| Female | 7/65 | 1.00 | |
| Male | 29/88 | **3.53 (1.44-8.67)** | |
| Time from HCT to COVID-19 | | | 0.005 |
| >12 m | 15/96 | 1.00 | |
| ≤12 m | 21/57 | **2.67 (1.33-5.36)** | |

## Autologous HCT

| | # Events/ # Evaluable | HR (95% CI) | P-value |
|---|---|---|---|
| Disease for HCT | | | 0.033 |
| PCD/MM | 12/69 | 1.00 | |
| Lymphoma | 12/34 | **2.41(1.08-5.38)** | |

**Other factors tested but not statistically significant:**

- ALLO: Immunosuppression within 6 months of COVID-19 diagnosis, Race and Ethnicity
- AUTO: Age, Gender, Time from HCT to COVID-19, Race and Ethnicity.

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Sharma et al, *Lancet Hematology, 2021*

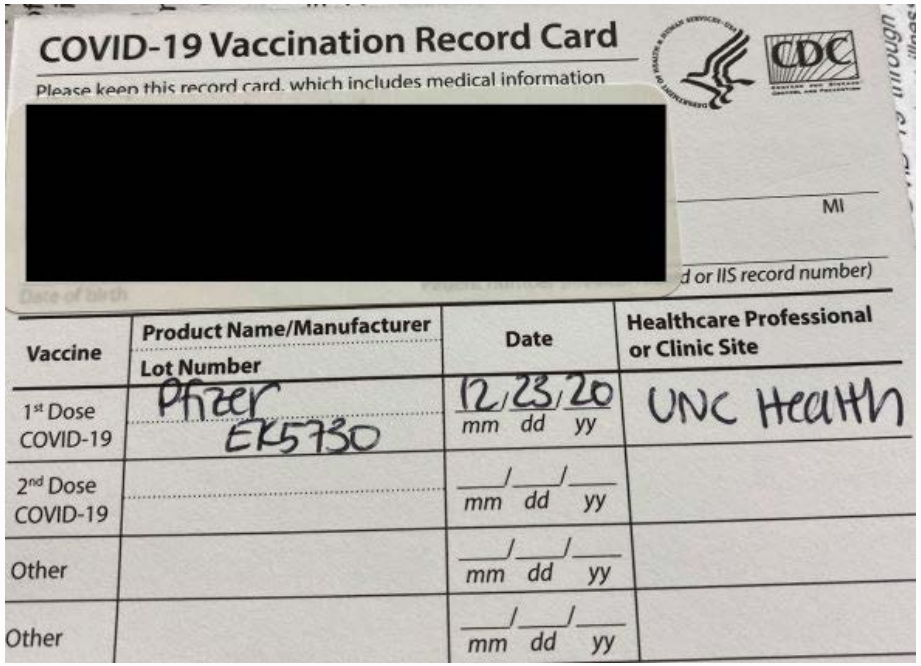
# Summary

- SARS-CoV-2
  - One of several Coronaviruses
- HCT/CT patients have higher risk of death compared to the general population
- Details on course and outcomes require coordinated data collection and analysis
- The transplant community responded quickly to this pandemic to provide guidance and to obtain data

# Summary

- Subsequent analyses to examine additional risk factors, co-infections, implications of pre-HCT COVID-19

- Hope is coming with the roll out of vaccinations
  - The efficacy of the vaccine in immunocompromised HCT/CAR-T patients is unknown



COVID-19 Vaccination Record Card

Please keep this record card, which includes medical information

[redacted]

MI

d or IIS record number)

| Vaccine | Product Name/Manufacturer Lot Number | Date | Healthcare Professional or Clinic Site |
|---|---|---|---|
| 1st Dose COVID-19 | Pfizer EK5730 | 12/23/20 mm dd yy | UNC Health |
| 2nd Dose COVID-19 | | __/__/__ mm dd yy | |
| Other | | __/__/__ mm dd yy | |
| Other | | __/__/__ mm dd yy | |

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THANK YOU FOR LISTENING
IF YOU HAVE ANY QUESTIONS I AM SURE GOOGLE WILL ANSWER THEM
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